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Contents on Inside Cover

American Heart Journal

CONTENTS FOR AUGUST, 1956

Editorial

Original Communications

Clinical Reports

Announcements

(Editorial and Business Communications on Page 20 of Advertising Section)

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American Heart Journal

VOL. 52 AUGUST, 1956 No. 2

Editorial

PRINCIPLES FOR DETERMINATION OF ELECTROCARDIOGRARHIC NORMAL STANDARDS

WITH the growth of clinical electrocardiography, reliable standards of normality have become increasingly important, but the volume of research on normal variability is very small as compared to that on disease and disorder. Further work on normal variability is essential.

Satisfactory progress has been made in the standardization of conventional leads and general ECG technique, but some factors, such as meal intake, are still ignored in the routine clinical electrocardiography and merit consideration.

In the following paragraphs, the principles for determination of electrocardiographic normal standards are briefly stated:

1. The criteria of clinical health, used by various authors for the selection of normal control groups, have varied widely from highly selected groups such as young aviators to noncardiac patients, even during the terminal stages of disease. The standards derived from such different groups are not comparable.

Normal standards should be based on samples sufficiently representative of clinically normal population, and there should be clearly defined criteria for definition of normality.

2. The population sample to which the standards refer should be precisely described, particularly in regard to items which have been shown to affect the ECG (age, sex, body weight). Other items (race, geographical region, climate, occupation), should also be considered in the description of groups, although the information of possible effects on the electrocardiogram is still scanty.

3. Normal standards derived from any particular group, although strictly valid only for this group, may have general application to other groups. The closer the similarity of the groups, the greater the validity of the standards will be. A breakdown into age, body weight, sex, and racial groups will make the standards more precise for any such classification, but there is still a large variety of factors to be studied and the application of "normal standards" even to apparently similar groups has still a certain margin of error.

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4. The combination of various samples in order to arrive at greater general validity is of doubtful merit if heterogeneous samples are used. In this case, the range in the standards for the combined group will be much wider than for any of the single groups, resulting in a much poorer differentiation between normal and abnormal.

5. The normal limits should be given in terms of the percentage of normal population included. Limits including 100 per cent of the normal population are not practical because a very large number of cardiac patients would also be included within such wide limits, resulting in a large percentage of false diagnoses of normality. Arbitrary limits including 95 to 98 per cent of normal population have been shown to be practically workable. The probability that an ECG item outside these range limits is due to pathology is significantly greater than the chance of a normal variation, but it is often not recognized that a small part (2 to 5 per cent) of normal population will, by definition, exceed the limits.

6. The normal limits should be determined from evaluation of the frequency distribution. The quite commonly used presentation of individual extremes, without analysis of the frequency distribution, has, at best, an approximate value for general orientation, but cannot be used as valid standards.

7. In the normal ECG standards for normal adults recommended by the Criteria Committee of the New York Heart Association,[1] many of the above principles have been ignored.

In view of the wide use of these criteria, a fairly detailed criticism may be useful.

A. The inadequacy of the normal standards for the adult population, given in Table IV, p. 178, is revealed by even superficial inspection. According to the table, the Q, R, and S waves may be zero in all three unipolar limb leads. This is a defect in the organization of the table. It is not indicated that a zero deflection in any one unipolar limb lead is never associated with a zero deflection in another unipolar limb lead.

More serious is the lack of consideration of the electrical position of the heart for determining the normal limits of unipolar limb leads. Lumping all heart positions together will lead to false diagnoses of normality. For instance, for the normal lower limit of T in aV_L a value of -4.0 is suggested, which might be acceptable for a vertical heart, but would be clearly abnormal for a horizontal heart with positive QRS in aV_L.

B. For the normal limits, individual extreme values of eight population samples were taken.[2-9] The extremes will vary with the size of the sample, all other factors being the same. The size of the samples for the various leads in the table varies between 30 and 594, so that the normal limits for the various leads are far from equivalent. This is demonstrated for the minimum and maximum T values in V_L of -1.0 and $+1.5$, from sixty-two subjects, as compared to -4.0 and $+6.0$ for aV_L, derived from 479 subjects. The difference is much greater than accounted for by the mean augmentation factor of 1.5. In one of the samples,[7] the number of subjects was twenty-five for V_1, V_3, and V_5, but fifty-two for V_2, V_4, and V_6.

Since the sample of Vaquero[5] of 500, including 338 adults over twenty years is the largest, it will determine the individual extremes in the combined groups; this means that the table refers essentially to the Mexican population rather than to the United States population. There is no a priori certainty that populations in different countries are electrocardiographically equivalent; statistically significant differences in the electrocardiographic age trends between Italian and Minnesota populations were recently found.[10]

C. It was noted above that a combination of various population groups is useful only when they are sufficiently homogeneous. The groups combined in Table IV could not have been more heterogeneous.

C 1. While the table refers to adults over 20 years of age, Sokolow and Friedlander's[8] sample with an age range from 1 to 60 years is included. Deeds and Barnes[6] sample ranges from 17 to 47 years. Only seventeen out of 151 subjects are over 50 years in Sokolow and Friedlander's group. In contrast, in Myers' group of fifty-two subjects, thirty-one were over 50 years with a total age range from 19 to 87 years. Due to the presence of statistically highly significant age trends between 20 and 50 years,[11] the limits for each group will vary with the age composition. One might argue that the inclusion of young and old people in some of the samples would make the table applicable to adult population over 20 years in general, without age specification. This would be true, however, only if the age distribution was controlled and analyzed. As it is, age is an uncontrolled factor in Table IV, seriously limiting its usefulness.

The same can be said for the sex distribution, varying from an all male sample of Kossmann and Johnston,[2] to a one-to-one male-female ratio in Deeds and Barnes' group.[6] In several of the samples, the sex distribution is not given.

In no sample is the relative body weight given, though this is a significant variable for the normal ECG.[11]

C 2. In most of the samples, normality is defined by negative findings in a clinical routine examination. However, Sokolow and Friedlander's sample is composed of a highly selected group of flying personnel as well as of a group of psychiatric patients. While the absence of clinical cardiovascular pathology is not doubted, emotional and psychiatric disorders may change the ECG.[12] An objection can be raised also against the inclusion of Myers' group of fifty-two autopsied cases,[7] who died from noncardiac disease. The heart was found normal on autopsy, but anatomic normality does not exclude functional changes. If the ECG's of this group were taken some time before the disease, the definition of normality would be very good. It is not stated when the ECG's were taken, and it appears more probable that they were taken while the patients were in the hospital. In nine patients with cirrhosis, cardiac decompensation was most likely, and this may be true also for seven patients with terminal pneumonia. Some of the patients with malignant tumors may have been in a state of malnutrition; any of these conditions, together with terminal electrolyte disturbance, may have affected the ECG, in spite of anatomic normality. This sample can hardly be considered as representative of normal population.

It is probably due to the inclusion of one or the other sample, not representative for normal adult American population, that a small negative T wave in

V_4 is still considered as normal, resulting in false diagnosis of normal in a large number of patients.

C 3. One should expect that at least the technique was identical in the various samples, but Deed and Barnes[6] used the C_R and C_F leads, while the table refers to the V leads.

It is felt that a revision of the ECG standards in adult population is needed.

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Original Communications

THE RELATIONSHIP BETWEEN THE BALLISTOCARDIOGRAM. CARDIAC MOVEMENT, AND BLOOD FLOW

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INTRODUCTION

KNOWLEDGE of the genesis of the ballistocardiogram is fundamental to its clinical interpretation. Considerable evidence relates the ballistic record to flow, and particularly to acceleration of the stroke volume.[1,2] Recent reports of increase in both amplitude and wave form definition following ligation of the venae cavae would indicate that the ballistocardiogram is unrelated to flow and solely the result of cardiac motion.[3,4]

There is general agreement that the ballistocardiogram is a force curve. A simple impulse of force, however, can produce any pattern of motion depending upon the mechanical system through which force acts. The vibration properties of the subcutaneous tissues dominate the relationship between cardiac force and body motion; the ballistocardiograph must therefore be designed to minimize this influence. Studies of the body as an oscillating system were therefore undertaken, and the results applied to the design of new ballistocardiographs, with mechanical constants selected to eliminate tissue distortion.[5-7] With physical factors largely controlled, the output of these new "aperiodic" systems may be cautiously interpreted in terms of discrete physiologic events. This study was, therefore, undertaken to investigate the relationships between cardiac motion, central blood flow, and the "aperiodic" ballistocardiogram.

METHODS

The animal ballistocardiograph consisted of a 1.4-pound, nylon covered, rigid aluminum frame suspended to a natural frequency of 0.5 cycles per second and free to move in the horizontal plane. A piston moving in steam cylinder oil provided proper damping. Animals were placed back down and fixed to metal

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by clamps which engaged bone at shoulder and pelvic girdles. Acceleration was measured directly with Calidyne or crystal accelerometers.* A flat frequency response for the body-platform system has been demonstrated experimentally for the range 1.0 to 16 cycles per second, and by theoretic analysis for the range 0.5 to 35 cycles per second.[8] Filter output was further amplified and recorded at paper speed 50 mm. per second on a Sanborn polyoscillograph. Similar results were obtained from lateral, longitudinal, and, in some instances, anteroposterior records for each experimental manipulation to be described. Extremely large dogs were occasionally available and necessitated the use of a heavier platform intended for humans. In all cases the ratio of animal weight to platform weight was adequate to preserve a flat frequency response in the range of interest.

Animals were anesthetized with intravenous pentobarbital, intubated, and cannulated in the usual fashion. When balloon catheters were employed, recording lumina were located peripherally. In certain instances pure mechanical responses of the circulation were desired. To this end autonomic paralysis was obtained with hexamethonium, spontaneous respiration eliminated with curare, and denitrogenation effected with 100 per cent oxygen by resuscitator. Such a preparation could tolerate five minutes of apnea without anoxia or significant hypercapnia, and provided a stabile ballistocardiogram, free of respiratory artifact morphologically comparable to control traces with anesthesia alone.

Aortic blood flow was measured with a new strain gauge flow meter based on the principle of the hydrometric pendulum.[9] Its output is proportional to linear velocity of flow, and when differentiated, to acceleration of blood past the meter. A "T" cannula prevented change in aortic cross section; volume flow could therefore be obtained by integration.

RESULTS

1. *Normal Animal Ballistocardiogram.*—Dog ballistocardiograms resemble those of humans recorded with similar apparatus. Since wave form varies somewhat with the instrument and with the time derivative of motion to be recorded, no attempt is made to name deflections.

Normal records consist of three major waves following closely in time. The first wave has presystolic as well as systolic components. Its summit follows the onset of ventricular depolarization by 0.09 to 0.11 second. The second wave peaks 0.05 to 0.07 second later. Wave one precedes the anacrotic limb of the carotid pressure pulse by 0.06 second; wave two is synchronous with it. The third wave is long, complex, and variable. Its beginning is synchronous with the first vibrations of the carotid incisura, approximately 0.30 second after electrical systole. With the heavier platform time from ventricular depolarization to the peak of wave two is 0.20 to 0.22 second with the delays of other deflections in proportion.

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*Crystal accelerometers may be obtained from Mr. John Frank, 1301 Shawnee, Yellow Springs, Ohio.

The amplitude of wave two is usually maximal in longitudinal records, waves one and three in lateral or anteroposterior records. All three are demonstrable as separate simultaneous motions in frontal and sagittal planes.

Each individual wave represents the vector sum of forces which may change in amplitude, direction, and phase. Partial summation or cancellation of adjacent major waves occasionally occurs; this is particularly true for waves one and two in longitudinal records. The resulting alterations in wave form can be extremely misleading unless a bidirectional recording system of proper frequency response permits the identification of significant notches and changes of slope.

Thus the normal ballistocardiogram consists of three complex, interrelated events, which follow closely in time.

2. *Control of Venous Return.*—This group of experiments was designed to demonstrate the effect of graded obstruction to inflow at various sites on ballistic amplitude and wave form.

A. *Obstruction of the caval veins:* Experiments similar to those described by Cossio and Eddleman[3,4] were performed under controlled conditions. In six animals both thoracic venae cavae were intermittently obstructed by inflation of catheter balloons. In every instance ballistic force decreased to 50 per cent of control within fifteen seconds and, subsequently, stabilized slightly above noise level. Wave two was almost completely abolished; waves one and three persisted at reduced amplitude. Pressure rose in both caval systems, and carotid diastolic and pulse pressures dropped abruptly. In dogs with intact nervous systems, reflex hyperpnea introduced large respiratory artifacts, and cardiac rate increased slightly. With release of obstruction control amplitude and wave form were regained within four seconds.

Separate occlusion of the venae cavae elicited variable responses. In the intact animal, systolic forces usually increased slightly during superior vena caval occlusion and decreased during inferior vena caval occlusion, though opposite responses were occasionally observed in the same or in different preparations. Following curarization and autonomic blockade the response became consistent; obstruction of either caval vein decreased systolic amplitude, inferior vena caval obstruction regularly producing the more pronounced response (Fig. 1).

B. *Inflow obstruction at the right atrium:* Inflation of an atrial balloon to sufficient volume elicited responses identical to those observed when both venae cavae were occluded; wave two was reduced to a small remnant and waves one and three decreased in amplitude. At lesser balloon volumes intact animals increased the amplitude of waves one and two, sometimes quite markedly. The significance of this increase is discussed in section 4B. Wave form was unaffected by tricuspid regurgitation induced by stretching the auriculoventricular ring. Reflex responses to balloon inflation were more vigorous, though qualitatively similar to those initiated by vena caval occlusion. After complete autonomic blockade wave two regularly decreased at balloon volumes and filling pressures which previously had induced an increase, emphasizing the importance of inotropic reflex changes. After balloon deflation systolic force increased within

three beats and stabilized at control amplitude. Though bradycardia occurred in intact preparations, auricular premature contractions at control cycle length indicated that force had changed independently of rate. In those experiments in which venous hypertension and reduction in ballistic amplitude were produced by balloon inflation, sudden deflation was followed by the appearance of large "V" waves in the atrial pulse and abnormally large diastolic ballistic waves.

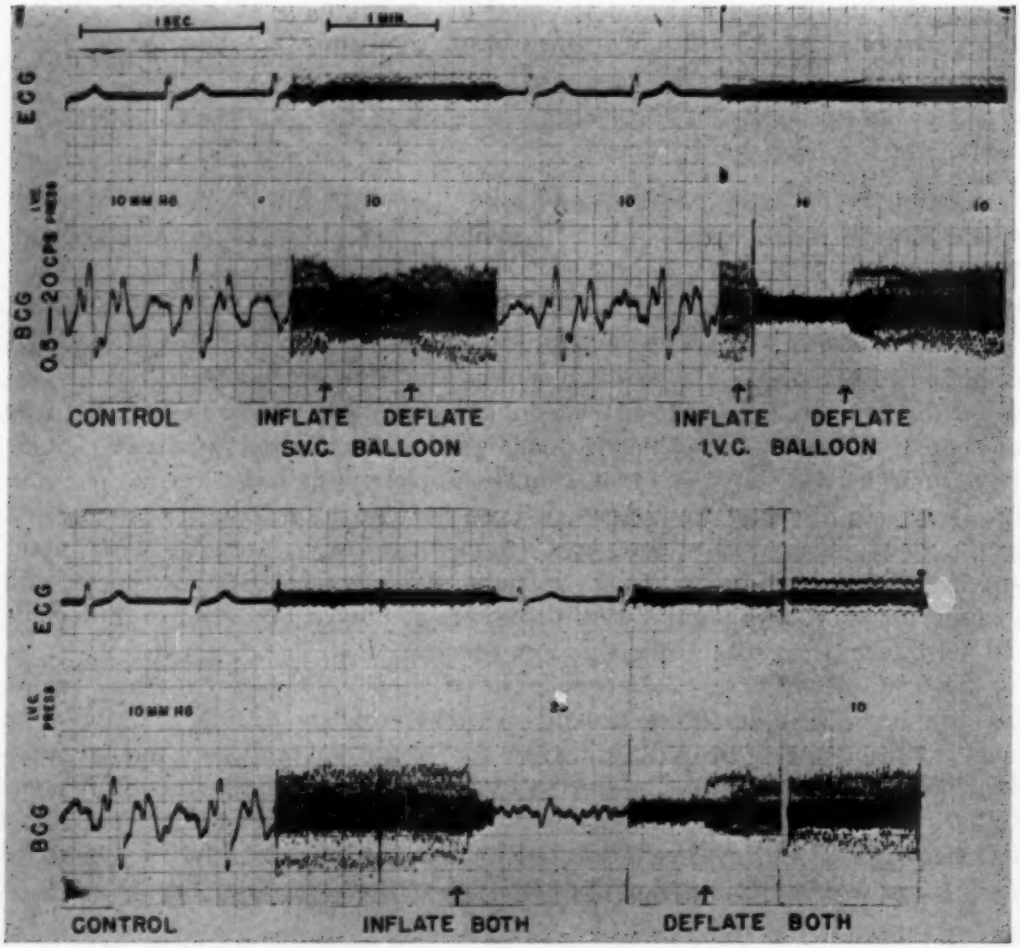


Fig. 1.—The effect of obstruction to venous return after curarization and autonomic blockade.

C. *Hydropericardium:* Acute hydropericardium is of interest because it impedes cardiac motion as well as venous return.

A polyethylene catheter was introduced through a pericardial stab puncture, sutured in place, and the chest closed. Curarization, autonomic blockade, and preoxygenation were accomplished and the entire three-minute experiment performed during apnea. When 80 c.c. of saline had been injected into the pericardial sac, central venous pressure rose, waves one and two decreased in amplitude, and a new diastolic force appeared. Similar abnormal diastolic waves

have been observed clinically.[10] An abrupt rise in venous pressure occurred at 120 c.c. injected volume and all forces declined to the noise level of the apparatus. Prompt return to control wave form followed withdrawal of fluid. Unlike simple obstruction to venous inflow, pericardial tamponade eliminated both cardiac motion and blood flow, and abolished the record completely.

D. *Effect of premature contractions:* Premature contractions afford an opportunity to observe the effect of abbreviation of diastolic filling time. In a dog with ventricular coupling the interval between premature and sinus beat was 0.31 second. The major deflections of the sinus beat should, therefore, have been practically completed before the arrival of ballistic impacts originated by the premature contraction. The diastolic interval separating any two sinus beats, however, was not appreciably distorted. Thus, when filling time is inadequate, force is small and wave form bizarre. With sufficiently long coupling, however, the shape of the premature contractions is identical to that of the basic rhythm.

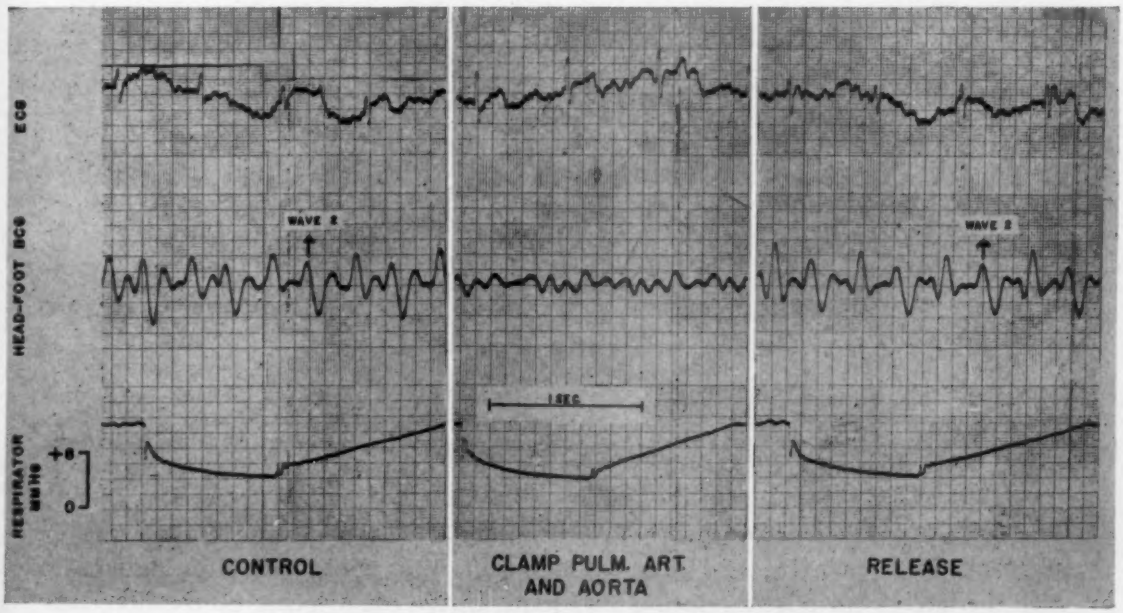


Fig. 2.—The response to complete obstruction to arterial outflow.

3. *Control of Arterial Outflow.*—The effects of decreased outflow and decreased venous return should be similar on those components of the ballistocardiogram which are related to flow. Changes in the time course of contraction secondary to change in resistance might also be expected to alter ballistic forces originated by cardiac motion.

A. *Complete pulmonary and aortic obstruction:* Heart and great vessels were exposed though the left fifth intercostal space and clamps applied across the main stem of the pulmonary artery and ascending aortic arch. During occlusion waves two and three could not be identified. Though presystolic

components of wave one decreased markedly, systolic components remained unchanged or increased. Prompt return to control amplitude and wave form followed release of obstruction (see Fig. 2).

Separate occlusion of aorta and pulmonary artery also decreased wave two. Though it would be of considerable interest to estimate the relative contribution of right and left ventricle separately, technical difficulties inherent in simple clamping experiments do not justify such quantitative conclusions.

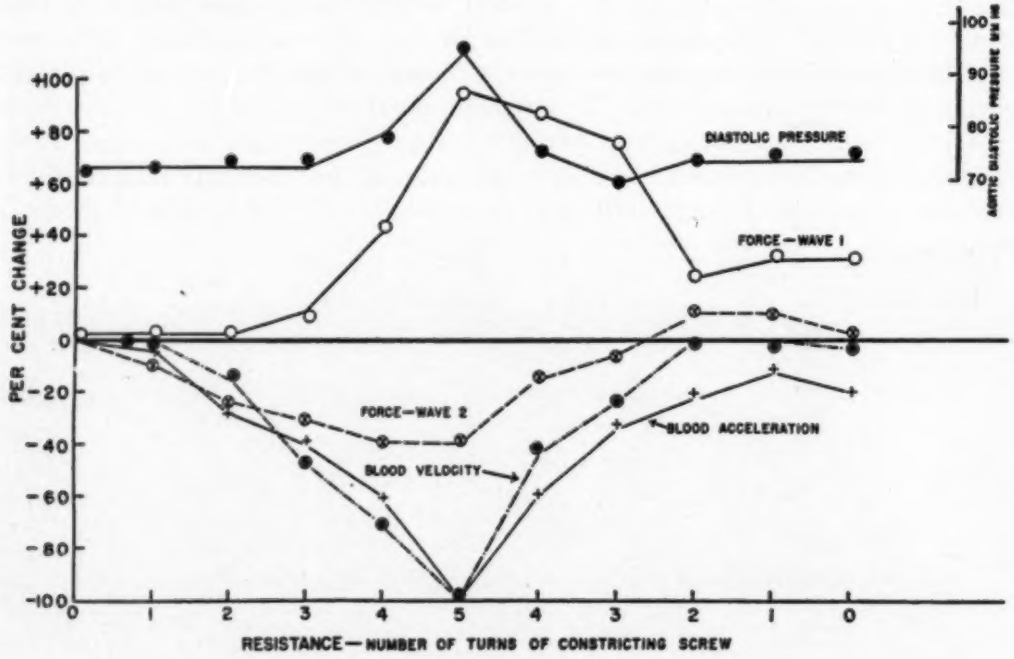


Fig. 3.—Hemodynamic effects of semiquantitative obstruction of descending aorta by means of a screw clamp. Abscissa indicates resistance in terms of number of turns of a constricting screw clamp. Progressive constriction proceeds to complete obstruction (5) followed by recovery as constriction is released to the starting point. Note that wave 2 varies directly, wave 1 inversely with blood flow.

B. *Graded obstruction of the descending aorta:* In two large hounds aortic pressure, flow velocity, and flow acceleration were measured simultaneously with the ballistocardiogram during semiquantitative constriction of the descending aorta distal to the meter. Fig. 3 relates per cent change in these variables to resistance, expressed as number of turns of a constricting screw clamp. Because aortic cross section is constant at the meter, volume flow is proportional to velocity. As resistance is increased, velocity, acceleration, and wave two decrease proportionately until flow falls below 50 per cent of control. Velocity and acceleration then drop sharply to zero, but wave two persists at approximately half control amplitude. Wave one on the other hand remains constant until flow has decreased markedly, then exhibits a brisk 100 per cent rise. Opposite changes are observed with release of obstruction.

Note that wave two varies directly, wave one inversely with blood flow. The acute increase in resistance probably reduced stroke volume as well as descending aortic flow. The decreased amplitude of wave two therefore repre-

sents concomitant decrease in stroke volume and stroke acceleration. Failure of wave two to fall below half its control amplitude indicates that significant forces are contributed by flow in other vessels and/or by cardiac motion. The increase in wave one may be related to increase in cardiac mass and to positive inotropic responses initiated by cardiac dilatation.

C. *Exsanguination and replacement transfusion:* In the absence of circulating blood volume the ballistocardiogram can only be due to cardiac motion.

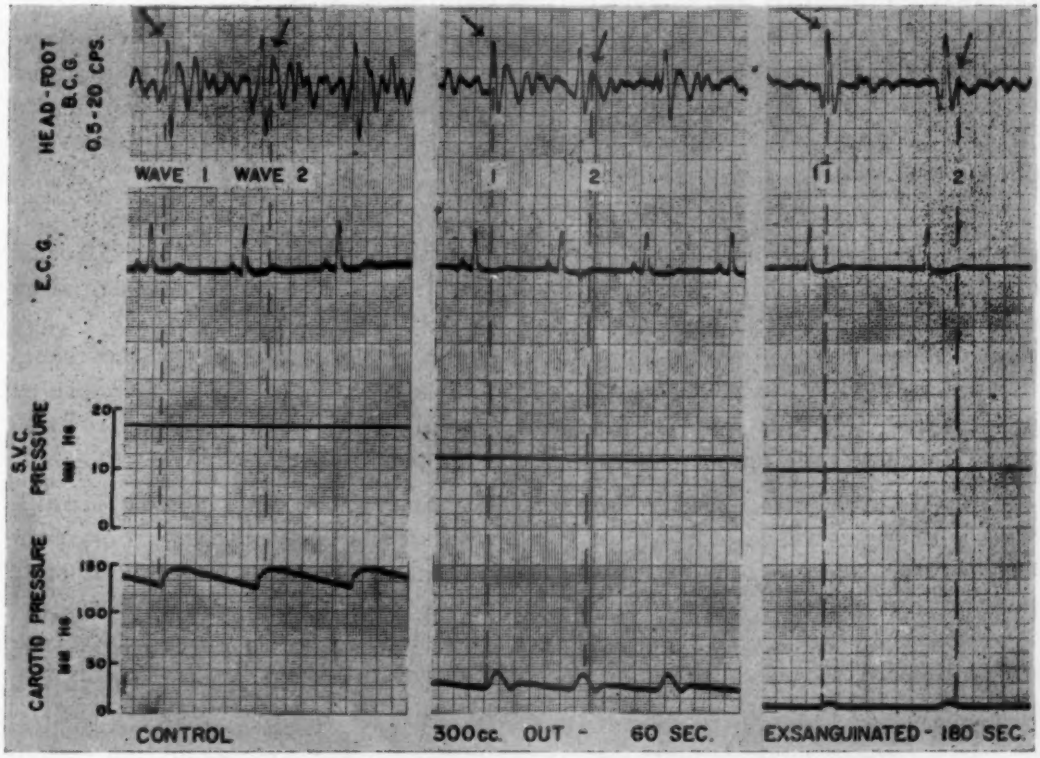


Fig. 4.—The effect of rapid arterial hemorrhage. Note that complete exsanguination almost abolishes wave 2 but wave 1 remains unchanged.

By means of a vacuum pump complete exsanguination could be achieved within 180 seconds; a compressed air source applied to the collection bottle permitted reinfusion within 90 seconds. The rapid time course of hemorrhage and reinfusion permitted repeated observations in the complete absence of flow without irreversible impairment of myocardial function. Fig. 4 illustrates the response of a 10.5 kg. dog. After 100 c.c. had been removed, arterial pressure fell slightly, central venous pressure remained constant, and all ballistic deflections increased in amplitude. The significance of this increase will be discussed in conjunction with Fig. 5. When 300 c.c. had been removed wave two had fallen to half its control amplitude; complete exsanguination practically abolished waves two and three, but wave one persisted unchanged.

D. *Intravenous air injection:* Effective arterial flow may also be eliminated by reducing the stroke volume to froth. While air was being injected into the brachial vein sinus rate increased from 100 to 200 per minute, and ballistic ampli-

tude decreased abruptly. This would not be expected as a rate or anoxic effect and only minor T-wave changes were observed in the electrocardiogram. The most dramatic feature was the increase in respiratory rate from 10 to 98 per minute, or approximately control heart rate. The resulting artifacts could easily have led to the erroneous conclusion that cardiac force had increased in the absence of flow, had reference variables not been simultaneously recorded. Actual ballistic amplitude was revealed before tachypnea had fully developed and after curarization had eliminated the respiratory artifact.

4. *Importance of Acceleration of Cardiac Ejection.*—Ballistic force is proportional to the product of mass of heart muscle and/or stroke volume, and acceleration. Experiments previously described deal primarily with acute changes in mass. Acceleration is equally important and may or may not vary directionally with stroke volume.

A. *The ballistocardiogram of the cold blooded heart:* The heart weight and stroke volume of a 15 kg. alligator snapping turtle are approximately 1/10 that of a 15 kg. dog. The stroke acceleration of the turtle, however, measured as rate of change of linear velocity in the common arterial trunk, is but 1/2500 that in the aorta of the dog. Thus the turtle force ballistocardiogram represents the product of adequate mass and negligible acceleration. It is therefore of interest that no ballistocardiogram could be recorded for the turtle even at 5,000 times standard gain and with the frictional damper removed.

B. *Inotropic responses during partial obstruction to venous return:* In animals with intact vasomotor reflexes, stretching of the venae cavae and particularly of the right atrium by balloon inflation increases systolic force despite concomitant decrease in venous return. When positive inotropic reflexes are interrupted by autonomic blockade the same obstruction to venous return reduces systolic force because the reduced stroke volume can no longer be compensated by an increase in its acceleration.

C. *Hemodynamic changes during hemorrhage:* The exsanguination experiments described in 3C provide other demonstrations of increased systolic force in the presence of reduced stroke volume.

In Fig. 5 the onset of hemorrhage is marked by a sharp drop in diastolic pressure. Pulse pressure decreases slightly, and pulse contour reflects the resistance change. Central venous pressure falls initially, then rises slowly toward control level. These changes are accompanied by a 50 per cent increase in the amplitude of wave two, which is maintained until 250 c.c. or approximately two thirds the total blood volume are removed. Arterial and venous pressures then fall precipitously and the pressure pulse assumes the contour characteristic of an underdistended reservoir. Note that force does not drop below control amplitude until twenty seconds after this final decline in central pressures. Reinfusion results in prompt rise and overshoot of all variables.

The instantaneous velocity (a function of acceleration) produced by a constant impulse of force is inversely proportional to mass, in this case the mass of blood accelerated. In addition to inertia, motion of blood is opposed by viscous fluid friction and vessel elasticity. Therefore, if contractility and cycle length

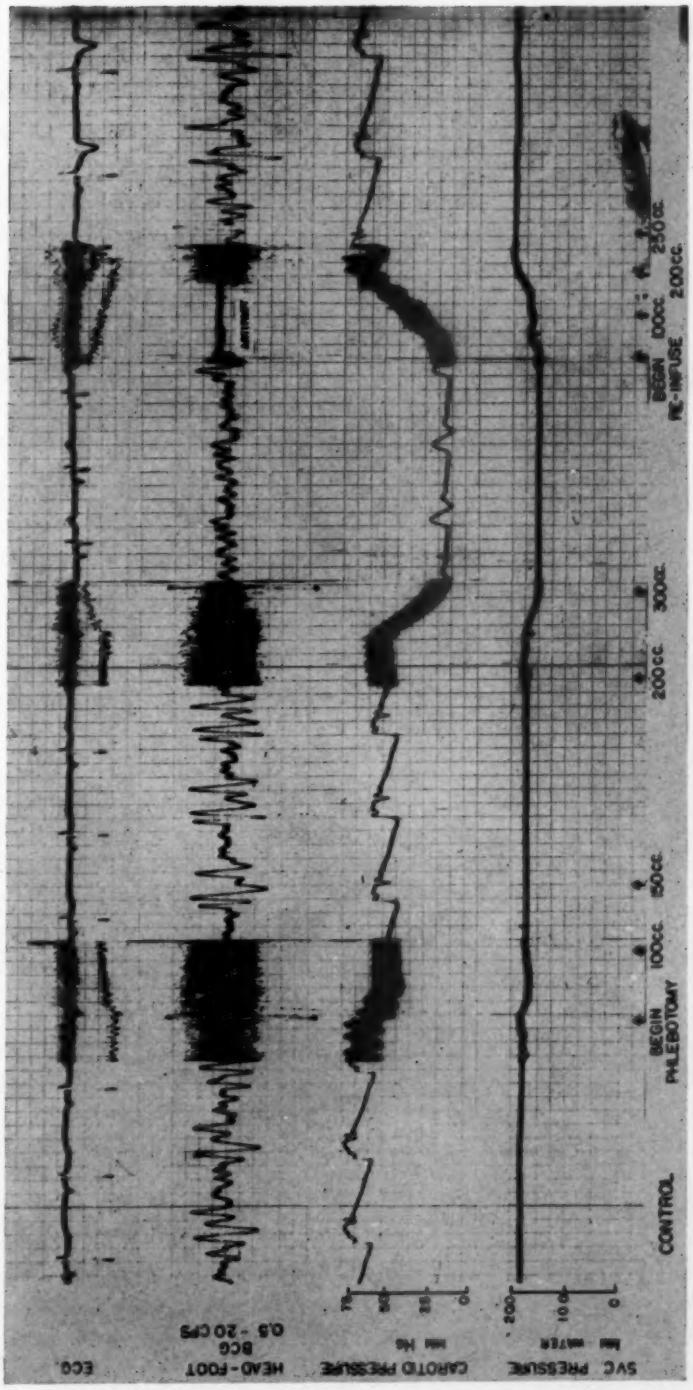


Fig. 5.—The time course of exsanguination and replacement transfusion in a preparation with intact vasomotor reflexes. Discussion in text.

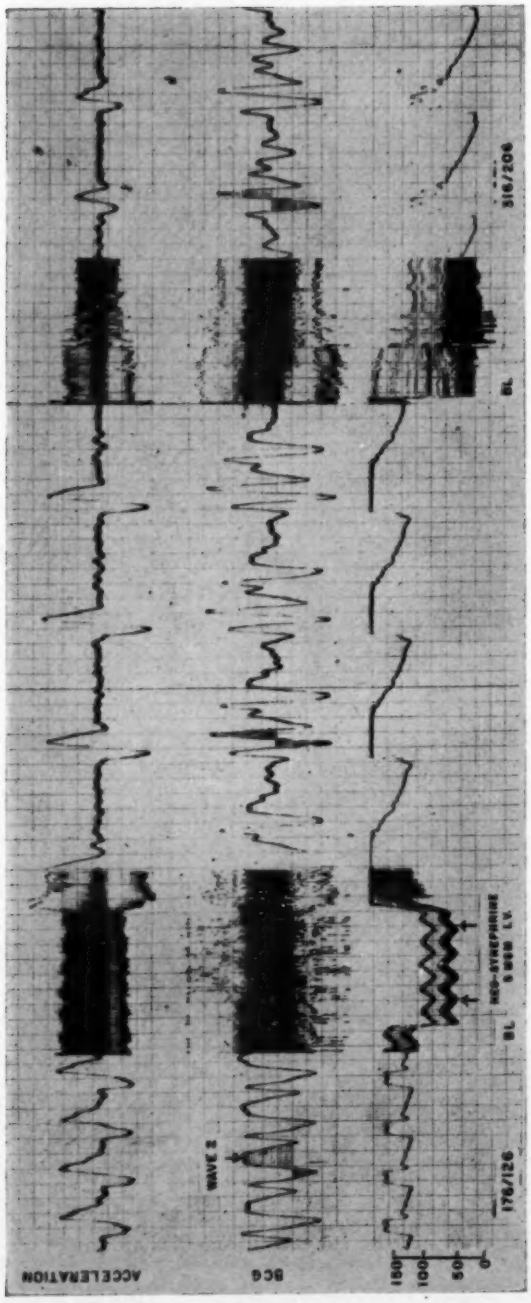


Fig. 6.—Effect of 5 mg. of Neosynephrine on ballistic amplitude and blood acceleration in the descending aorta. *B. L.* indicates "base line" shift. Discussion in text.

(impulse) do not decrease, blood acceleration in the central arteries is inversely proportional to peripheral resistance and to stroke volume.[11] The initial decrease in central venous and pulse pressures and change in pulse contour suggest a decrease in stroke volume; the terminal fall in central pressures is definitely secondary to reduced stroke volume. Use of animals with intact vasomotor reflexes assures an increase in contractile force under stress. The presence of this inotropic response is confirmed by the overshoot in ballistic amplitude following reinfusion. Cycle length is not appreciably decreased until the final pressure fall. Though intense vasoconstriction undoubtedly occurred, suction applied to the femoral artery produced an immediate fall in diastolic pressure and resistance.

In summary a larger impulse is applied to a smaller mass against a lowered resistance. The increased acceleration of blood which results is sufficient to increase ballistic force in the presence of a reduced stroke volume. As emphasized in section 3C, however, the most vigorous acceleration is ineffective when the stroke volume is sufficiently small.

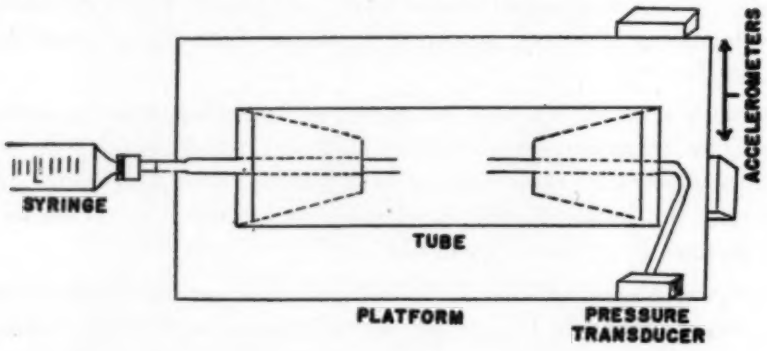
D. *Effect of Neosynephrine:* In therapeutic doses Neosynephrine increases peripheral resistance, cycle length, stroke volume, contractility, heart size, and venous pressure.[12]

Fig. 6 illustrates the response of a spontaneously breathing closed chest dog to 5 mg. of Neosynephrine. The ballistocardiogram was recorded from the heavier platform simultaneously with aortic pressure and descending aortic blood acceleration. Blood pressure rose briskly from 176/126 to 316/206 mm. Hg and cardiac rate fell from 188 to 84 per minute. During the initial pressure rise blood acceleration and wave two increased sharply. As diastolic pressure stabilized, however, blood acceleration rapidly fell below control, and despite the increased stroke volume indicated by the wide pulse pressure and bradycardia, wave two showed a parallel decline. Though wave two did not drop below control, this has been observed in other dogs and in man. The final effect on the amplitude of wave two depends upon the degree of increase in stroke volume relative to the fall in stroke acceleration.

Note that the large diastolic ballistic wave has no equivalent in aortic flow. In dog and man venous hypertension and diastolic gallop sounds are common at peak drug effect, suggesting that the diastolic wave may be a venous phenomenon. Increased amplitude of a standing wave initiated by the sudden increase in resistance could also produce such vibrations, as discussed in section 5.

5. *Ballistic Forces Originated by a Standing Wave.*—The order of magnitude of ballistic forces which could be generated by a standing wave in the absence of flow was investigated by means of a model. A soft rubber tube, 0.6 mm. wall thickness, 46 mm. outside diameter, and 85 cm. long was distended with water and aligned in the long axis of the animal platform. Longitudinal and lateral acceleration was measured at gain usually required for animal ballistocardiography. Water was injected manually in 20 c.c. increments at an acceleration insufficient to deflect the table. Abrupt cessation of flow generated a grossly visible standing wave, accompanied by rolling, torsional movements, and by ballistic forces

which corresponded well to changes in intraluminal pressure (see Fig. 7). Lateral vibrations were uniformly larger than longitudinal ones, whether the tube was free, tied down with tape, buttressed with sand, or twisted to the shape of the aortic arch. The experiment demonstrates the relationship between ballistic forces and motion of a center of gravity, which need not necessarily be associated with flow. The demonstration that lateral forces may originate in a straight tube indicates that change in vessel orientation is not essential for the explanation of forces perpendicular to the long axis of the body.



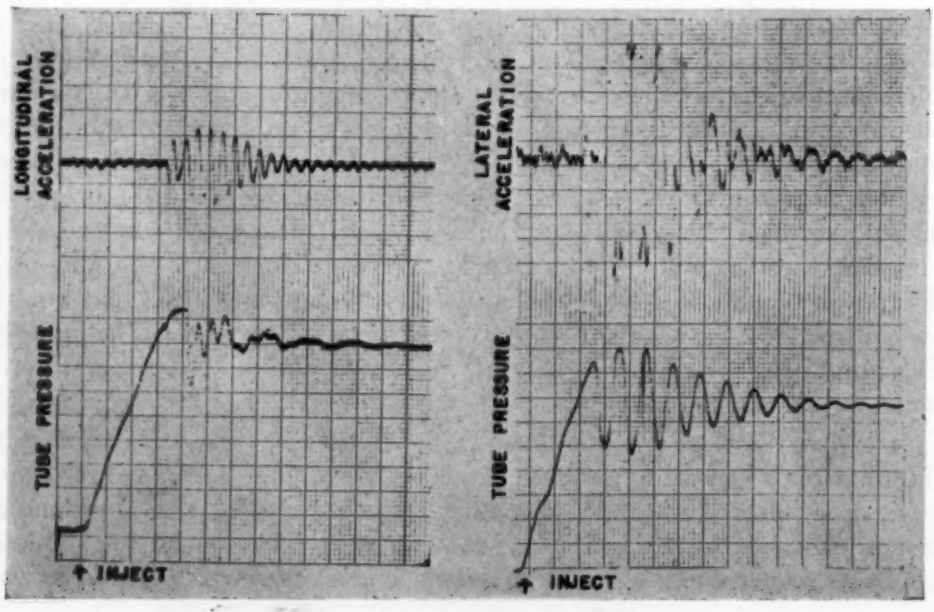


Fig. 7.—Ballistic forces originated by a standing wave. Note that platform motions begin when flow ceases and correspond well to changes in intraluminal pressure.

6. *Effect of Atrial Contraction.*—Complete heart block affords an opportunity to observe the isolated atrial ballistocardiogram. In a 36-year-old man with congenital complete heart block atrial systole appears as small sinusoidal vibrations. Beats with fortuitously normal time relationships demonstrate that, at normal heart rates, wave one represents partial summation of the effects of atrial and ventricular contractions.

The amplitude of the atrial wave is maximal when it happens to coincide with the rapid filling phase of the ventricle, and falls off rapidly for beats which occur later in diastole. This suggests that atrioventricular blood flow as well as cardiac motion contribute to the atrial wave.

DISCUSSION

The above experiments demonstrate in all instances that the ballistocardiogram is related both to cardiac motion and to blood flow, a finding at variance to the recent reports of Cossio and Eddleman.[3,4]

The direct body ballistocardiograph which these authors employed is distorted by tissue resonance, particularly when applied to the loose panniculus of the dog. When a single force is recorded with insufficient damping and a large resonance peak (in this case 3 cycles per second), in the frequency range of interest, forces slightly above or below resonance frequency fail to reach the transducer. Those which do set up after-vibrations which summate with or cancel subsequent forces originated by the heart. Each cardiac cycle, however, initiates several discrete forces which follow one another without pause, and which contain frequency components up to at least 20 cycles per second.[8] It is therefore impossible to interpret either the amplitude or wave form of direct body ballistocardiograms in terms of specific physiologic events unless tissue distortion is eliminated by a correcting electronic network.[5] Though the records of Eddleman are much improved by the use of sand damping, after-vibrations have been shown to be present when the technique is applied to the human cadaver[13] and would be expected to be even more troublesome in the living dog. Though no data as to the vibration properties of the dog in sand are as yet available, it is probable that a flat frequency response was not attained.

The necessity for lateral and anteroposterior records has been repeatedly demonstrated in this study. Late components of wave one and early components of wave two may be opposite in direction and often overlap, particularly in longitudinal records. In such cases the onset of wave two may appear as a notch or change of slope yet be clearly delineated in other projections. The use of sand fixation unfortunately limits measurement to one direction. Finally, Cossio's published records do not include reference variables. These may be of particular importance to separate the confusing effects of artifacts reflexly induced by the experimental procedure. Rapid forceful respiratory movements and direct effects upon ventricular function often made it impossible to interpret the response under test until autonomic blockade and respiratory arrest were accomplished.

Properly recorded, three independent groups of forces comprise the normal human or animal ballistocardiogram. The first wave preceeds ejection, and the late effects of atrial contraction are superimposed upon its early components. It is large when the heart is hypertrophied, dilated, or stimulated, and small when the heart is depressed or poorly filled. It persists in the complete absence of venous return, arterial flow, or circulating blood volume, and is therefore solely the result of cardiac motion. The loose coupling of heart to body shell probably accounts for its relatively small amplitude.

The second major wave is synchronous with ejection and is reduced to a small remnant by complete interruption of venous return at any site. In animals with intact reflex mechanisms partial obstruction to venous return may increase or decrease its amplitude depending upon the degree of obstruction, the intensity of reflex stimulation, peripheral resistance, and intrinsic myocardial factors. With complete autonomic blockade any significant decrease in venous return reduces its amplitude. The second wave is also practically eliminated by complete outflow obstruction, exsanguination, and reduction of stroke volume to froth. Insufficient diastolic filling time, inadequate acceleration of stroke volume, vasoconstriction, and heart failure decrease its amplitude; vasodilatation, increased stroke volume or stroke acceleration augment it. Ejection and change in cardiac size and center of gravity proceed together as an interrelated process. The above experiments demonstrate, however, that those cardiac motions which accompany ejection differ from those which precede ejection in that they generate negligible reaction force. Wave two may therefore be regarded as almost entirely the result of acceleration of a central arterial volume.

Wave three is a composite of several diastolic events. It is decreased by exsanguination, vasodilator drugs, outflow obstruction and air injection, and increased in hydropericardium, congestive failure, and acute vasoconstriction. It therefore seems related to large venous decelerations and to accelerations originated by the aortic standing wave. Forces generated by systolic stress of the elastic cardiac suspension could also contribute.

Since the ballistocardiogram is a force curve, reduction in mass of stroke volume may be readily overshadowed by an increase in its acceleration (Experiments 4B and 4C) and the most vigorous acceleration of a negligible stroke volume results in a small reaction force (Experiments 2A, 2B, 3A, 3C, and 3D). Similarly, poor acceleration of a normal or increased stroke volume also generates little force (Experiments 4A and 4D). Frequently, as in Experiments 2C, 2D, and 3B the ballistocardiogram reflects concomitant change in stroke volume and stroke acceleration.

SUMMARY AND CONCLUSIONS

1. Animal ballistocardiograms free of tissue distortion have been recorded during experiments designed to alter venous return, arterial outflow, circulating blood volume, and stroke acceleration.

2. Normal ballistocardiograms consist of three major waves:

A. The first wave is partly superimposed upon vibrations originated by atrial systole. It precedes ejection, persists in the complete absence of blood flow, and varies directly with heart size and vigor of contraction.

B. In normal subjects the second wave dominates the longitudinal ballistocardiogram. It is synchronous with ejection and reduced to a negligible remnant by complete interruption of blood flow. Its amplitude varies with both stroke volume and stroke acceleration.

C. The third wave is a complex of diastolic forces associated with venous flow, and oscillations originated by the aortic standing wave.

3. Reaction forces produced by the acceleration of a central arterial volume are largely responsible for the genesis of the ballistocardiogram; cardiac motion plays a secondary role. The physical and biologic factors responsible for the differences between these results and those of others are discussed.

SUMMARIO IN INTERLINGUA

Ballistocardiogrammas animal libere de distortiones texital esseva registrate durante experimentos in que esseva alterate le refluxo venose, le effluxo arterial, le volumine de sanguine circulante, e le acceleration del pulso. Le registrationes normal consiste de tres undas major. Le prime se superimpone partialmente super vibrationes originari in le systole atrial. Illo precede ejection, persiste in le complete absentia de fluxo, e varia directemente con le dimensiones del corde e le vigor del contractiones. Le secunde unda es synchrone con le ejection e es practicamente eliminate per le complete interruption del fluxo. Su amplitude varia directemente con le volumine e le acceleration del pulso. Le tertie unda es relationate con phenomenos venose e con oscillationes originari in le unda stationari aortic. Es discutite le factores physic e biologic que es responsabile pro le differentias inter iste resultatos e illos de altere autores.

We are indebted to Mr. W. W. von Wittern, who designed the ballistocardiographs and flowmeter. The continued interest and encouragement of Dr. Harvey Savely, Chief, Biophysics Branch, Aero-Medical Laboratory, is gratefully acknowledged.

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THE DIAGNOSTIC SIGNIFICANCE OF THE RESPIRATORY FLUCTUATIONS OF THE PULMONARY ARTERIAL PRESSURE IN MAN

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PULMONARY arterial pressure tracings in animals[1-4] and in man[5-9] show measurable respiratory fluctuations: in inspiration the pressure falls somewhat and in expiration it rises. Under normal conditions these fluctuations are small. However, in some cardiopulmonary disturbances the fluctuations may be significantly enhanced. Although the magnitude of the fluctuations depends in part on changes in intrathoracic pressures during respiration, it is possible that significant information concerning cardiopulmonary relationships might be obtained from a survey of data on the pressure changes in the lesser circulation. For this purpose, records obtained during right heart catheterization in man were analyzed.

METHODS

Records on a four-channel Sanborn Poly-Viso instrument were obtained during the course of catheterization of patients and normal subjects in the Hibse Heart Station of the Michael Reese Hospital.† The position of the catheter tip was noted by fluoroscopy. The distal end of the catheter was attached to a condenser type electromanometer (Sanborn).

Special attention was given to the pulmonary arterial pressure curves. These were calibrated with a zero level 5 cm. dorsal to the angle of Louis with the patient in the recumbent position. The tracings were analyzed by recording the end-diastolic and the peak systolic pressures of each cardiac cycle for at least 10 beats of an undisturbed run.

In most instances the pressure changes themselves were used to indicate the phase of the respiratory cycle; this was based on the generally accepted principle that the pressure within the chest falls in inspiration, and rises in expiration. Inspection of the pressure curves demonstrated that a fairly clear representation of the probable respiratory cycle could thereby be discerned. In several patients who carried out voluntary breath-holding maneuvers, the respiratory fluctuations vanished. In other patients on whom chest movements were recorded, there was, as ex-

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†We are indebted to the members of the Catheterization Unit who made these records available to us for study.

pected, a clear and consistent relationship between inspiration and a fall in pulmonary arterial pressure, and expiration and a rise in this pressure. In nine other patients (three normal, and six with rheumatic heart disease) the patterns of oral airflow were determined by means of spirometer or pneumotachygraph. The pneumotachygrams so obtained were planimetrically integrated to determine mean tidal volume.

In Tables I to V, VII, and VIII, the minimal (inspiratory) systolic and diastolic pressures are given on each of the patients and a summary table of the average data is given in Table IX. Addition of the respiratory fluctuations to these minimal levels gives values for the maximal (expiratory) systolic and diastolic pressures. When the protocols inscribed during catheterization indicated that respiratory disturbances were present, as occur in anxiety or crying, the data were excluded from the study.

TABLE I. NORMAL SUBJECTS

PATIENT	AGE (YEARS)	PAP_s	PAP_d	F_s	F_d	RHYTHM
E. H.	33	15	1	2	2	SR
E. B.	34	16	1	3	3	SR
R. B.	8	12	3	2	2	SR
W. H.	22	16	5	3	3	SR
W. L.	20	17	3	3	3	SR
R. M.	21	13	3	5	5	SR

PAP_s = Minimum systolic pulmonary arterial pressure (mm Hg).
PAP_d = Minimum diastolic pulmonary arterial pressure (mm Hg).
F_s = Systolic respiratory fluctuations (mm Hg).
F_d = Diastolic respiratory fluctuations (mm Hg).
SR = Sinus rhythm.

TABLE II. CHRONIC PULMONARY DISEASE WITHOUT PULMONARY HYPERTENSION

PATIENT	AGE	PAP_s	PAP_d	F_s	F_d	RHYTHM	REMARKS
L. K.	56	22	3	4	4	SR	emphysema ASHD
J. F.	50	14	−1	2	6	SR	kyphoscoliosis
J. C.	74	14	0	7	5	SR	emphysema, bronchiectasis
W. McH.	63	25	6	5	6	SR	emphysema, bronchiectasis

ASHD = Arteriosclerotic heart disease. Other symbols as in Table I.

TABLE III. CHRONIC PULMONARY DISEASE WITH CHRONIC COR PULMONALE

PATIENT	AGE	PAP_s	PAP_d	F_s	F_d	RHYTHM
D. L.	66	24	16	11	9	AF
S. K.	42	22	7	16	15	SR
I. G.	61	32	10	18	12	SR
V. R.	2	63	32	10	17	SR
B. H.	34	57	29	20	21	SR
W. D.	30	45	24	18	9	SR
C. D.		41	15	13	19	SR

AF = Auricular fibrillation. Other symbols as in Table I.

The records on fifty-nine patients had sufficient data for a satisfactory analysis. These were separated into groups depending on the final diagnosis, which was based on clinical and catheterization data, and in some instances on surgical intervention.

TABLE IV. SYSTEMIC HYPERTENSION

PATIENT	AGE	PAP_s	PAP_d	F_s	F_d	RHYTHM	SYSTEMIC BLOOD PRESSURE (MM. HG.)
N. McR.	44	55	10	9	10	SR	210/132
B. G.	58	61	25	11	8	AF	240/135
H. G.	31	53	24	5	9	SR	164/120
A. G.	69	18	3	2	3	SR	260/160

Symbols as in Tables I and III.

TABLE V. RHEUMATIC HEART DISEASE

PATIENT	AGE	PAP_s	PAP_d	F_s	F_d	RHYTHM	REMARKS
A. H.	52	18	7	9	5	AF	M. S.
S. J.	19	19	7	4	4	SR	M. S., M. I.
S. C.	27	24	6	4	2	SR	M. S.
M. S.	33	24	5	4	6	SR	M. S.
S. McN.	11	13	4	3	2	SR	M. S.
J. G.	53	16	7	5	4	AF	M. S., M. I.
E. F.	36	16	4	4	4	SR	M. S., A. S.
J. B.	38	25	13	4	5	SR	M. S.
B. G.	34	40	9	3	4	SR	M. S.
D. G.	33	40	24	6	5	SR	M. S., A. I.
W. B.	49	72	31	8	7	SR	M. S.
A. K.	47	65	31	21	8	AF	M. S., M. I., T. S., T. I.
M. L.	44	76	41	20	11	AF	M. S., M. I., T. I.
S. K.	46	90	40	10	9	AF	M. S., M. I.
S. J.	34	54	27	12	9	AF	M. S., A. I.
S. C.	34	46	20	7	10	SR	M. S., M. I.
R. B.	26	80	39	20	15	AF	M. S., T. S.
A. A.	37	45	17	19	19	SR	M. S., M. I., A. I., Asthma
L. H.	45	75	42	14	10	SR	M. S., M. I., A. I.

M. S. = Mitral stenosis, *M. I.* = Mitral insufficiency, *A. S.* = Aortic stenosis, *A. I.* = Aortic insufficiency, *T. S.* = Tricuspid stenosis, and *T. I.* = Tricuspid insufficiency. Other symbols as in Tables I and III.

RESULTS

1. *Cases Without Evident Cardiopulmonary Disease.*—Six cases were included in this category. These showed systolic pulmonary arterial pressures of 17 mm. Hg or less. The respiratory fluctuations of the pulmonary arterial pressure averaged 3/3 mm. Hg (systolic/diastolic), varying from 2 to 5 mm. Hg (Table I). A typical example is given in Fig. 1,*A*.

2. *Chronic Respiratory Disease.*—Four patients with chronic pulmonary disorders, the nature of which are given in Table II, and who had pulmonary arterial pressures in the range of normal, were studied. In these, respiratory fluctuations averaged 5/5 mm. Hg, ranging from 2 to 7/4 to 6 mm. Hg.

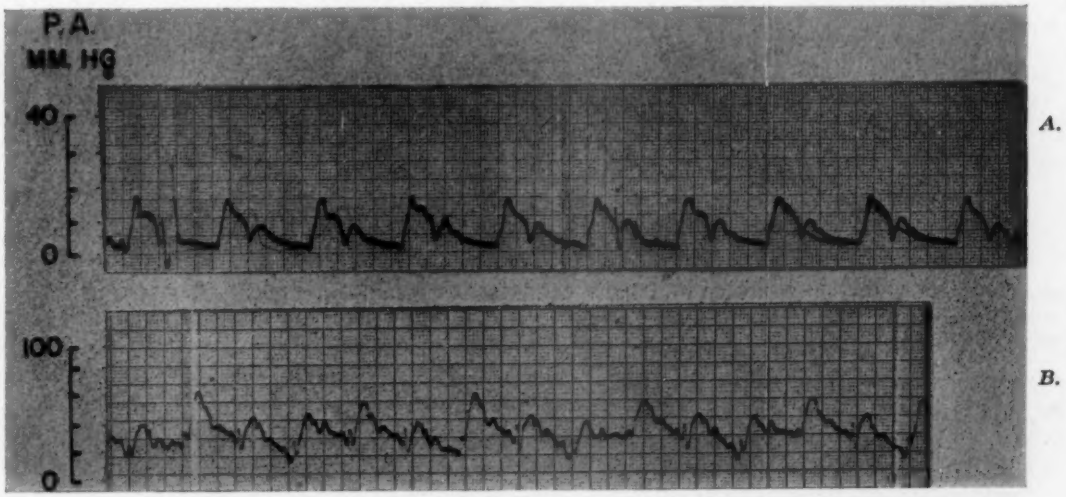

Fig. 1.—Pulmonary arterial pressure in *A* (Patient E. H.) who had no evidence of cardiopulmonary disease, and *B* (Patient C. D.) who had chronic cor pulmonale. *PA* refers to the pulmonary arterial pressure with calibrations as given. The distance between successive heavy lines is 0.2 second.

3. *Chronic Cor Pulmonale.*—Seven cases diagnosed as chronic cor pulmonale with elevated pulmonary arterial pressures had average fluctuations of 14/13 mm. Hg, ranging from 8 to 20/9 to 21 mm. Hg (Table III). A typical record is given in Fig. 1,*B*.

4. *Systemic Hypertension.*—Four patients with systemic hypertension were studied (Table IV). In three, the pulmonary arterial pressure as well as the respiratory fluctuations were greater than those found for the normal group. The respiratory fluctuations averaged 8/9 mm. Hg. One patient (A. G.) showed fluctuations of 2/3 mm. Hg; this patient also had a normal pulmonary arterial pressure. The record on patient N. McR. is shown in Fig. 2,*A*.

5. *Rheumatic Heart Disease.*—Nineteen cases with rheumatic heart disease were studied (Table V). Eight of these patients had inspiratory pulmonary arterial pressures of 25/13 mm. Hg or less; in all of these the respiratory fluctuations averaged 5/4 mm. Hg ranging from 3 to 9/2 to 6 mm. Hg. The remaining

eleven patients had pulmonary arterial pressures definitely in the abnormal range. In all but two of these the respiratory fluctuations were significantly outside that seen in the normal individual.

In the eleven cases with definitely elevated pulmonary arterial pressures the respiratory fluctuations averaged 13/13 mm. Hg, ranging from 6 to 21/5 to 19 mm. Hg. Records on one of these patients are illustrated in Fig. 2,*B*, in which simultaneous pneumotachygraphic registration of oral air flow, electrocardiogram,

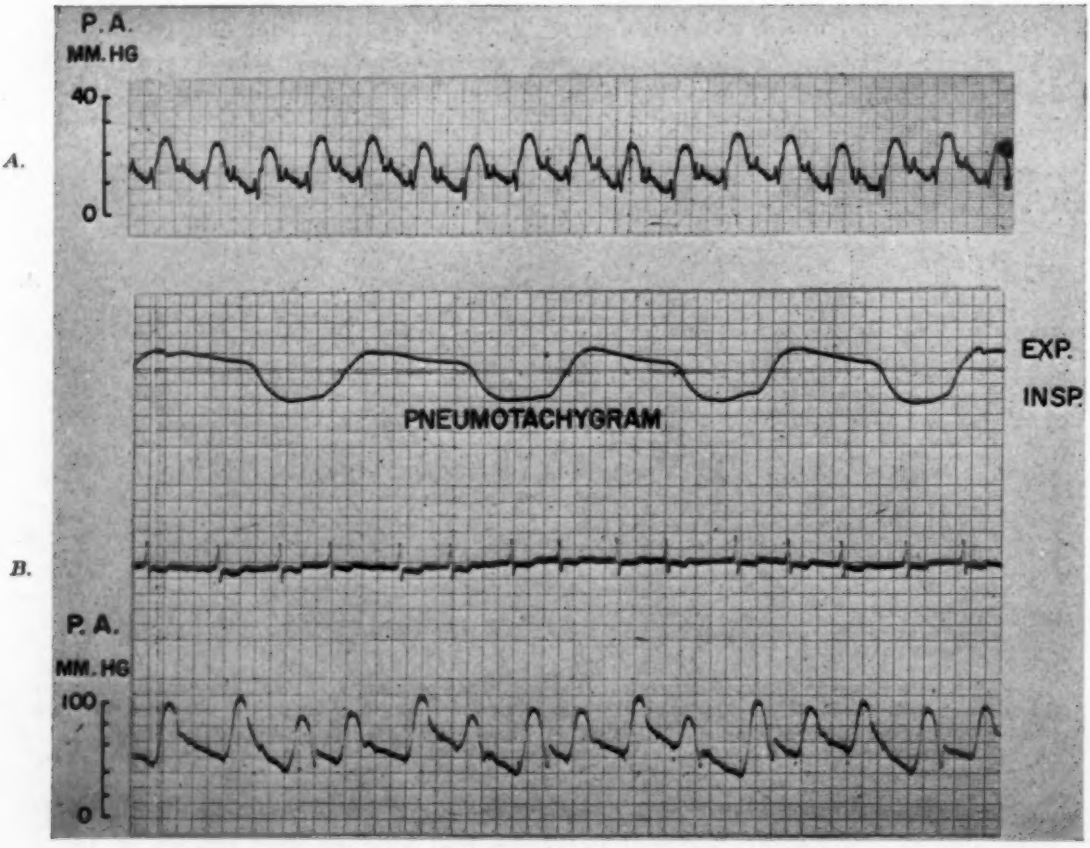

Fig. 2.—*A*, Pulmonary arterial pressures in Patient N. McR. who had systemic arterial hypertension. Conventions as in Fig. 1. *B*, Clipping from a record on Patient R. B. who was diagnosed as having rheumatic heart disease with predominent mitral stenosis. The pneumotachygram demonstrates the periods of expiration (*EXP.*) and inspiration (*INSP.*) as noted. The electrocardiogram is given as the middle tracing. The pulmonary arterial pressure is shown as the lower tracing. Conventions as in Fig. 1.

and pulmonary arterial pressure are displayed. One case could be considered as intermediate between the two groups since the pulmonary arterial diastolic pressure was only 9 mm. Hg, although the systolic was 40; in this instance the respiratory fluctuations were 3/4 mm. Hg.

In general, patients with an elevated pulmonary arterial diastolic pressure also had respiratory fluctuations outside the normal range (Fig. 3), and there was a relationship between the height of the pulmonary arterial pressure and the magnitude of the respiratory fluctuations in this pressure. It was demonstrated

that these fluctuations in the pulmonary arterial pressure were not related to the mean tidal volume, since this volume was relatively comparable to that of the controls (Table VI).

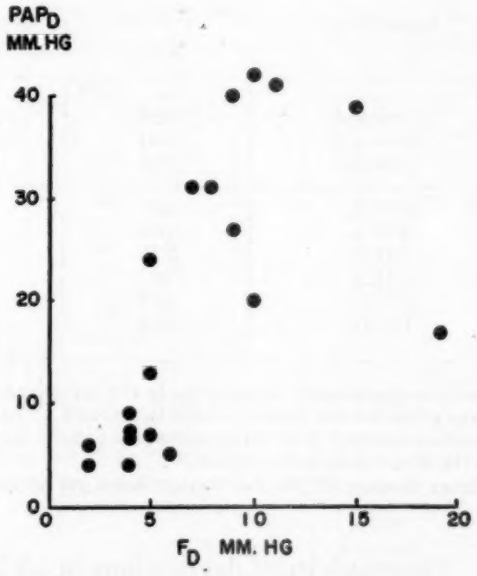

Fig. 3.—The relationship between the minimal diastolic pulmonary arterial pressures and the respiratory fluctuations in nineteen patients with rheumatic heart disease. It can be seen that with elevated pulmonary arterial pressures there is a definite tendency for the respiratory fluctuations to be enhanced.

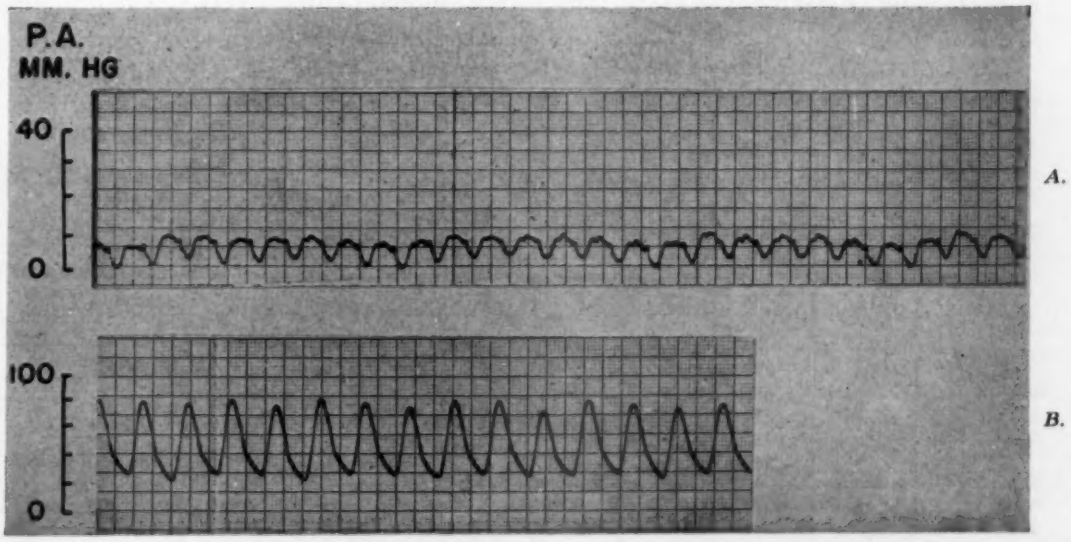

Fig. 4.—*A*, A blood pressure record from the pulmonary artery in a patient (M. C.) with valvular pulmonic stenosis. *B*, A blood pressure record from the pulmonary artery in a patient (R. H.) with ventricular septal defect and pulmonary arterial hypertension.

6. *Pulmonic Stenosis.*—Ten patients diagnosed as having pulmonic stenosis with or without other malformations were studied (Table VII). The pulmonary arterial pressure was low, averaging 11/2 and ranging between 5 to

TABLE VI. TIDAL VOLUMES COMPARED WITH RESPIRATORY FLUCTUATIONS IN THE PULMONARY ARTERIAL PRESSURE

PATIENT	DIAGNOSIS	MEAN TIDAL VOLUME		F_d
		c.c.	c.c./M.² BSA	
W. H.	Normal	520	327	3
W. L.	Normal	490	250	3
R. M.	Normal	570	300	5
A. K.	RHD	461	283	10
M. L.	RHD	708	389	21
W. B.	RHD	776	504	7
L. H.	RHD	843	529	19
R. B.	RHD	628	336	15
H. H.	RHD	641	317	12

It should be noted that the respiratory fluctuations in the pulmonary arterial pressure differ somewhat in this table from data given for the same patients in Table V. This may be due to the fact that the subjects had just previously swallowed an intraesophageal balloon for the determination of pressures in this viscus. Patient H. H. is not included in Table V.

***RHD* = Rheumatic heart disease; *M.²BSA* = Square meter per body surface areas. Other symbols as in Table I.**

20/0 to 6 mm. Hg. The respiratory fluctuations in all instances were 6/5 mm. Hg or less. A clipping from the record on patient M. C. is shown in Fig. 4,*A*.

7. *Ventricular Septal Defect With Pulmonary Arterial Hypertension.*—Nine cases having a diagnosis of ventricular septal defect with pulmonary arterial hypertension (Eisenmenger's syndrome) were studied (Table VIII). The pulmo-

TABLE VII. PULMONIC STENOSIS WITH OR WITHOUT ASSOCIATED ANOMALIES

PATIENT	AGE	PAP_s	PAP_d	F_s	F_d	RHYTHM	REMARKS
R. F.	11	12	4	2	5	SR	Tetralogy of Fallot
N. Z.	11	10	4	3	4	SR	Tetralogy of Fallot
J. W.	4	5	1	4	3	SR	Infundibular stenosis, ? I.A., I.V. defects
H. H.	23	11	0	3	3	SR	Tetralogy of Fallot
M. G.	7	5	0	6	4	SR	Tetralogy of Fallot
C. G.	11	16	4	3	3	SR	Acyanotic tetralogy of Fallot
M. C.	6	6	0	2	3	SR	Valvular pulmonic stenosis
F. W.	9	20	1	3	3	SR	Infundibular pulmonic stenosis, I.V. defect
S. W.	19	12	3	4	4	SR	Valvular pulmonic stenosis
H. W.	10	11	6	4	3	SR	Tetralogy of Fallot

***I. A.* = Interatrial and *I. V.* = Interventricular. Other symbols as in Table I.**

nary arterial pressures averaged 85/51, ranging from 55 to 115/21 to 74 mm. Hg. The respiratory fluctuations were 8/6 mm. Hg or less, averaging 5/5 in this group. A clipping from the record on patient R. H. is given in Fig. 4,*B*.

TABLE VIII. PULMONARY HYPERTENSION WITH VENTRICULAR SEPTAL DEFECT

PATIENT	AGE	PAP_s	PAP_d	F_s	F_d	RHYTHM
R. P.	4	73	40	4	5	SR
J. P.	5	81	52	3	3	SR
J. P.	23	65	74	5	4	SR, VPS
A. H.	6	115	74	5	5	SR
M. F.	19	103	54	5	5	SR
D. K.	5	94	56	8	5	SR
D. McE.	3	55	34	6	6	SR
R. H.	5	64	21	5	3	SR
J. M.	30	115	55	5	5	SR

VPS = Ventricular premature systoles. Other symbols as in Table I.

TABLE IX. AVERAGE RESPIRATORY FLUCTUATIONS OF PULMONARY ARTERIAL PRESSURE

GROUP	NO. OF CASES	MEAN MINIMAL PAP (MM. HG)	MEAN F_s (MM. HG)	MEAN F_d (MM. HG)
Normal Subjects	6	15/3	3	3
Chronic pulmonary disease				
(A) without pulmonary hypertension	4	19/2	5	5
(B) with pulmonary hypertension	7	41/19	14	13
Systemic hypertension				
(A) without pulmonary hypertension	1	18/3	2	3
(B) with pulmonary hypertension	3	56/30	8	9
Rheumatic heart disease				
(A) without pulmonary hypertension	8	19/8	5	4
(B) with pulmonary hypertension	11	63/29	13	9
Pulmonic stenosis with or without associated anomalies	10	11/2	3	3
Ventricular septal defect with pulmonary hypertension	9	85/51	5	5

PAP = pulmonary arterial pressure. Other symbols as in Table I.

DISCUSSION

A summary of the average fluctuations in the pulmonary arterial pressure in the various conditions presented is given in Table IX.

The mechanisms of the respiratory fluctuations in the pulmonary arterial pressure appear to be complex. Disturbances in respiration can obviously augment these fluctuations, since the pulmonary arterial pressure must be considered in terms of its environmental pressure level, i.e., the pressure inside the chest. As the intrathoracic pressure rises with expiration and falls with inspi-

ration, this pressure must be impressed on that in the pulmonary artery. The pulmonary arterial pressure also reflects the pumping action of the right ventricle as evidenced by the stroke output. The stroke output may fluctuate during the respiratory cycle with an enhanced flow during inspiration and a decreased flow during expiration. The rate of run-off determines the fall in pressure during diastole and this in turn depends on the resistance to flow posed by the pulmonary arteries, arterioles, capillaries, and venous system.

Changes in the resistance to blood flow through the lungs can result from respiratory activity. For example, the pressure acting on the pulmonary capillaries (intra-alveolar pressure) presumably falls during inspiration and rises during expiration. Such pressure changes acting on these thin-walled vessels can obviously affect resistance and consequently produce some fluctuations in the pulmonary arterial pressure. Other mechanisms may also be operative.

In the present study no attempt is made to separate these effects. However, the degree of the respiratory fluctuations in the various conditions cited may provide evidence for some of them. In any event, the differences in the degree of the fluctuations have interest since they seem to permit differentiation of certain groupings of cardiopulmonary disease.

Valsalva-like breathing as in crying can cause pressure elevations of as much as 50 mm. Hg during attempted expiration.[10,11] Other respiratory disturbances as occur in chronic pulmonary or cardiac diseases may also heighten the oscillations. This effect would seem to be clear in severe emphysema with pulmonary arterial hypertension caused primarily by a progressive reduction in the size of the pulmonary capillary bed. In such cases the pulmonary arterial pressure variations probably reflect the increased excursions of intrathoracic pressure engendered by the increased impediment to air flow and by the decreased lung compliance.

The findings in rheumatic heart disease and in systemic hypertension bear a similarity to the data obtained in chronic cor pulmonale. All but two of such patients who had marked pulmonary arterial hypertension also had increased respiratory fluctuations (Fig. 3). In such instances the pulmonary hypertension would appear to depend primarily on a heightened left atrial (pulmonary arterial wedge) pressure and pulmonary venous congestion due to valvular obstruction or left ventricular incompetence. Organic or spastic changes in the pulmonary arterioles may also be implicated,[18,19] but available evidence suggests that these may be secondary to the primary pulmonary congestion[20-25] and hypertension, and are present only occasionally. The cause of the enhanced fluctuations in such cases is obscure. Increased resistance to air flow from the lungs during expiration, whether operating via passive or active mechanisms, may also participate by producing relative air entrapment during this phase.

In patients with pulmonary hypertension and ventricular septal defect, the results stand in sharp contrast to the preceding groups. Despite marked pulmonary arterial hypertension, the respiratory fluctuations were within the normal range. Inspection of published tracings obtained on patients with Eisenmenger's syndrome[26] also demonstrates minimal respiratory fluctuations despite severe pulmonary arterial hypertension. In these cases it is known that the major resistance to blood flow through the lung is in the precapillary region, that is, in the pulmonary arterial and arteriolar tree.

In pulmonic stenosis with or without associated anomalies the precapillary resistance is at or near the pulmonary valve and, as might be expected, the respiratory fluctuations were small.

The present analysis suggests that measurements of the magnitude of the respiratory fluctuations in the pulmonary arterial pressure may have value in distinguishing those conditions which have a primary precapillary resistance from those in which the resistance lies in or beyond the capillaries (Table IX).

SUMMARY

The pulmonary arterial pressure tracings in fifty-nine catheterized patients were studied to determine the degree of respiratory fluctuations. In normal subjects the respiratory fluctuations were small, averaging about 5 mm. Hg. In patients with chronic cor pulmonale there was a tendency to an increased degree of respiratory variations in the pulmonary arterial pressures, especially in those patients in whom pulmonary arterial pressure was high. Heightened respiratory fluctuations were also seen in patients with systemic arterial hypertension or with rheumatic heart disease. A relationship between the levels of the pulmonary arterial pressure and the degree of the respiratory fluctuations could be demonstrated in this general group of patients.

By contrast, patients with Eisenmenger's syndrome or with pulmonic stenosis and associated anomalies had respiratory fluctuations within the normal range. This is particularly striking in the Eisenmenger patients since these had normal respiratory fluctuations despite severe pulmonary arterial hypertension.

The mechanisms which may be responsible for these respiratory oscillations are discussed briefly. It is suggested that attention given to the fluctuations may be of assistance in assaying the presence of precapillary resistance in the pulmonary vasculature.

SUMMARIO IN INTERLINGUA

Le registrationes del pression pulmono-arterial in cinquanta-nove catheterisate patientes esseva studiate pro determinar le grado de fluctuation respiratori. In subjectos normal le fluctuationes respiratori esseva parve; lor magnitude median esseva circa 5 mm. Hg. In patientes con chronic corde pulmonal il habeva un tendentia de augmento in le grado del variationes respiratori in le pressiones pulmono-arterial, specialmente in ille patientes in qui le pression pulmono-arterial esseva alte. Augmentate fluctuationes respiratori esseva etiam notate in patientes con systemic hypertension arterial o con rheumatic morbo cardiac. In iste gruppo general de patientes il esseva possibile demonstrar un relation inter le nivellos del pression pulmono-arterial e le grado del fluctuationes respiratori.

Del altere latere, patientes con syndrome de Eisenmenger o con stenosis pulmonic e anomalias associate habeva fluctuations respiratori intra le limites del norma. Iste facto es specialmente frappante in le caso del patientes con syndrome de Eisenmenger: illes habeva normal fluctuationes respiratori in despecto de sever hypertension pulmono-arterial.

Es presentate un breve discussion del mechanismos que es possibilemente responsabile pro le occurrentia de iste oscillationes respiratori. Es stipulate que attention prestate a tal fluctuationes es possibilemente de adjuta in probar le presentia de resistentia precapillar in le vasculatura pulmonar.

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ADENOSINE NUCLEOTIDE LEVELS IN CARDIAC ARREST

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A FINAL event in muscular contraction is probably the action of adenosine triphosphate (ATP) on actomyosin of excited muscle. Since cardiac arrest must ultimately be due to a disruption of this system, the amounts of adenosine nucleotides were determined in cardiac muscle from dogs in cardiac arrest due to hypoxia which was gradually increased during a period of one hour or longer. This method of ascertaining deficiencies in intermediary metabolism is pursued with the hope that information obtained will point to proper corrective measures.

METHODS

Dogs were anesthetized with 2 per cent Nembutal and were then supplied with an oxygen-nitrogen mixture through a closed circuit in which carbon dioxide was removed. While respiration was maintained manually at a rate of 16 excursions per minute, thoracotomy was performed, and the heart observed carefully. At intervals of ten minutes the rate of flow of oxygen, which was started at 400 c.c. per minute, was reduced by 50 c.c. per minute, whereas a flow of 2 liters of nitrogen per minute was maintained throughout the experiment. In another series of dogs, samples of muscle were obtained ten to twenty minutes after administration of Nembutal, and an adequate oxygen supply was maintained at all times.

In both groups of dogs, samples of muscle were quickly obtained from the left ventricle and extraction procedures were then carried out in the cold. After weighing, the muscle was homogenized in 3 ml. of 1.5 N perchloric acid. Each sample was centrifuged and washed once with distilled water; afterward the supernatant was neutralized and allowed to stand over-night in the refrigerator. The precipitate was then removed, and the sample was placed on a formate, ion-exchange column[2,3] of Dowex X-10 resin, 200 to 400 mesh, from which fine and coarse particles had been removed. Formic acid and mixtures of ammonium formate were then added consecutively, and 5 ml. volumes of eluate were col-

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lected by means of an automatic fraction collector shown in Fig. 1. First, 2 N formic acid solution was added slowly to the mixing flask containing 250 ml. distilled water; then the solution was changed to 4 N formic acid at tube 80, to 0.2 M ammonium formate in 4 N formic acid at tube 100, and to 0.4 M ammonium formate in 4 N formic acid at tube 180.[4] The optical density of each fraction was measured at both 260 and 275 mμ in 1.0 cm. quartz cells, using a Model DU Beckman spectrophotometer. The respective amounts of AMP (adenosine monophosphate), ADP (adenosine diphosphate), and ATP were calculated from these readings. The fraction containing each nucleotide had been identified in previous studies[1] with known samples and double eluent systems.

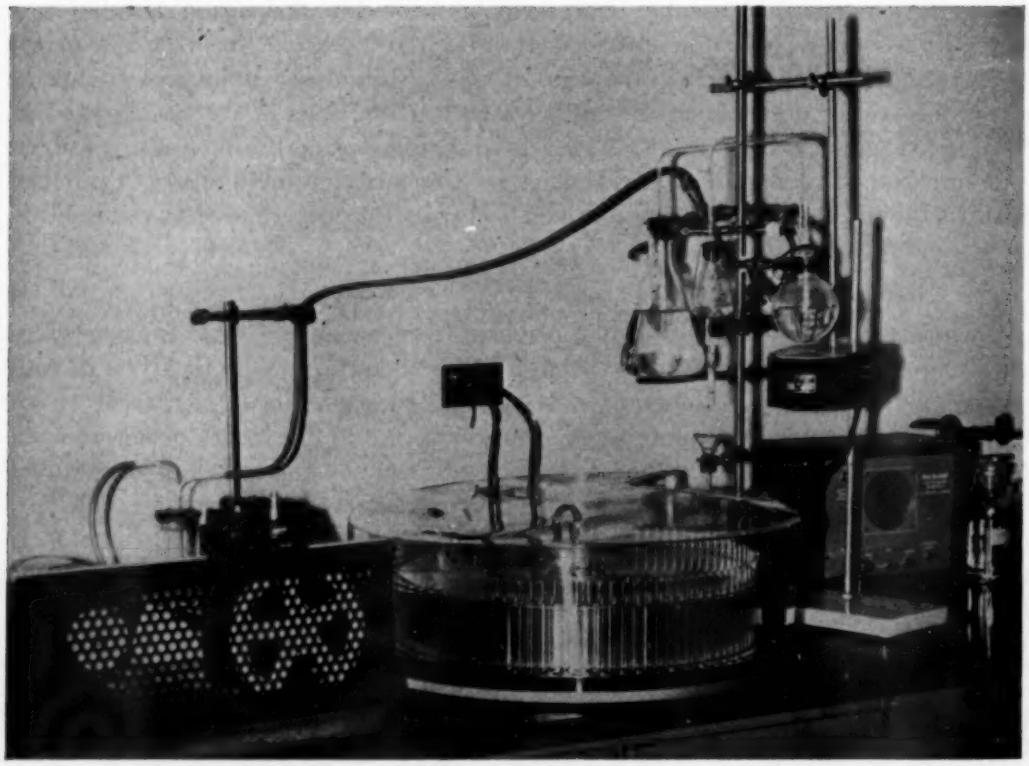

Fig. 1.—In this apparatus for separating adenosine nucleotides from homogenates of cardiac muscle, increasing concentrations of formic acid and ammonium formate in formic acid are added, under pressure, to a formate, ion-exchange column while measured quantities of eluate are collected automatically. The nucleotide content is then calculated from ultraviolet absorption measured spectrophotometrically.

RESULTS

In all eight dogs studied, hypoxia led to cardiac arrest in diastole. The average heart rate was 160 beats per minute up to a period shortly before cardiac standstill. The heart dilated, beats became less forceful as cyanosis increased during the last 10 to 20 minutes, and any reduction in oxygen flow proved critical during this period. Cardiac massage without increasing oxygenation failed to re-establish the heart beat in those animals in which it was tried.

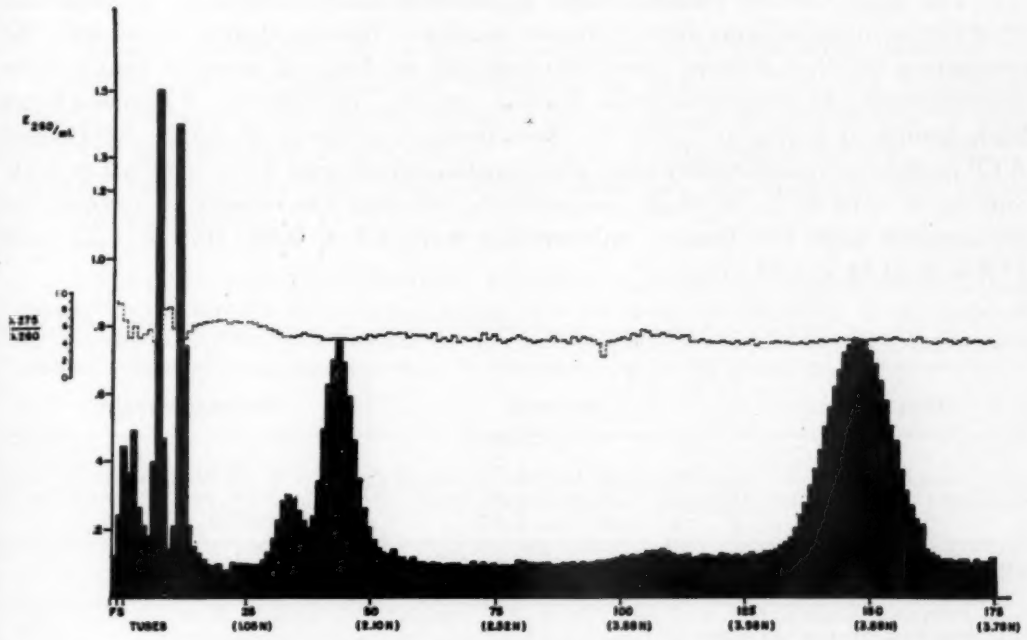

Fig. 2.—Absorption (E_{260}/ml.) of fractions from caninė myocardium from one of the dogs without treatment. AMP is the third of six large peaks, ADP the fifth, and ATP is the last.

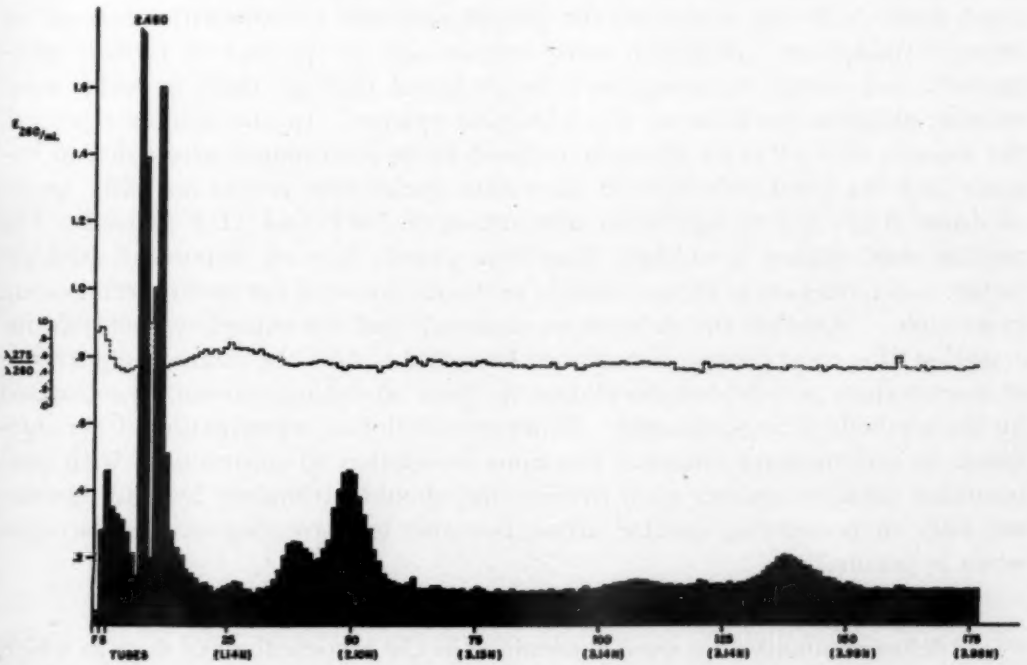

Fig. 3.—Comparison of peaks 5 (ADP) and 6 (ATP) in this histogram showing absorption (E_{260}/ml.) of fractions from a sample of myocardium obtained immediately after cardiac arrest to those in Fig. 2 reveals diminished amounts of ADP and ATP in arrest. The average content of AMP is also found to be diminished when results for the entire group of fourteen dogs are compared.

The most striking change found in the adenosine nucleotides is reduction of ATP in myocardium from arrested hearts. This is clearly illustrated by comparing graphs showing spectrophotometer readings of samples taken from experimental and control animals (Figs. 2 and 3). Results for all samples from both groups is given in Table I. The average amounts of AMP, ADP, and ATP in eight samples immediately after cardiac arrest were 4.6 ± 0.50, 6.1 ± 0.54, and 7.1 ± 1.18 M × 10^{-4}/Gm. respectively, whereas the respective amounts in six samples from functioning myocardium were 7.1 ± 0.58, 10.8 ± 1.21, and 18.1 ± 1.50 M × 10^{-4}/Gm.

TABLE I. ADENOSINE NUCLEOTIDE LEVELS (M × 10^{-4}/GM.)

NUCLEOTIDE	CONTROL	CARDIAC ARREST
AMP	7.1 ± 0.58*	4.6 ± 0.50
ADP	10.8 ± 1.21	6.1 ± 0.54
ATP	18.1 ± 1.50	7.1 ± 1.18
Total	36.0 ± 1.80	17.8 ± 1.49

*Standard error of the mean.

DISCUSSION

Energy for myocardial contraction may be provided through high-energy, phosphate bond exchange as ATP is dephosphorylated. ATP is then reconstituted from ADP by means of the phosphocreatine system with cleavage of creatine phosphate. Although other nucleotides are present in human myocardium and energy exchange may be mediated through them as well,[1] most existing evidence pertains to the adenosine system. In the studies reported, the amount of ATP is significantly reduced in myocardium in arrest due to hypoxia and the total reduction in adenosine nucleotides is due not only to diminished ATP, but to significant diminution of AMP and ADP as well. The method used makes it unlikely that hypercapnia was an important etiologic factor, and reduction in oxygen supply probably initiated the events terminating in asystole. Whether the deficiencies demonstrated are entirely responsible for cessation of cardiac contraction cannot be stated. Also the relative importance of deamination and dephosphorylation in these alterations cannot be estimated by the methods of analysis used. However, continued investigation of derangements in intermediary chemical reactions in relation to contraction, with concomitant trials to correct such deficiencies, should ultimately lead to success, not only in preventing cardiac arrest but also in correcting this catastrophe when it occurs.

SUMMARY

Adenosine nucleotides were determined in the myocardium of dogs in which cardiac arrest occurred as a result of hypoxia. When the results were compared to similar values for dogs without treatment, adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) were found to be diminished significantly during cardiac arrest.

SUMMARIO IN INTERLINGUA

Esseva determinate le nucleotidos adenosin in le myocardio de canes in le quales occurreva arresto cardiac resultante de hypoxia. Quando le resultatos esseva comparate con simile resultatos pro canes sin arresto cardiac il esseva trovate que adenosinotriphosphato (ATP), adenosinodiphosphato (ADP), e adenosinomonophosphato (AMP) esseva diminuite significativemente durante le arresto cardiac.

I wish to thank Dr. Van R. Potter for his advice concerning application of the ion-exchange method to this problem during a visit to the McArdle Memorial Laboratory of the University of Wisconsin which was made possible through the courtesy of Dr. Harold Rusch. Also I am indebted to Mrs. E. Rosenbohm and Mrs. T. Overman for technical assistance.

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THE EFFECTS OF INSULIN-INDUCED HYPOGLYCEMIA IN PATIENTS WITH ANGINA PECTORIS

Before and After Intravenous Hexamethonium

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INTRODUCTION

THE effects of insulin-induced hypoglycemia on the cardiovascular system and the electrocardiogram have been extensively studied and well documented in normal subjects[1] but not in patients with angina pectoris. The transitory changes in the electrocardiogram observed in normal subjects after the administration of insulin consisted of lowering and broadening of the T waves, depression of the S-T segments, lengthening of the Q-T interval, and occasionally disturbances of conduction and of rhythm, including sinus arrhythmia, extrasystoles, or auricular fibrillation. These electrocardiographic disturbances have been attributed to the direct action of hypoglycemia itself and/or to its indirect effects on the sympathoadrenal system with the release of epinephrine into the circulation.

Clinical observations and case reports in the literature[2-5] suggest that hypoglycemia resulting from not only large, but even small doses of insulin used in the treatment of diabetic patients with coronary artery disease may precipitate attacks of angina, or even coronary thrombosis. Since there is no documented experimental data to substantiate whether and how hypoglycemia per se may induce episodes of coronary insufficiency in patients with coronary artery disease, this study was undertaken. It was found that insulin-induced hypoglycemia produced certain alterations in the electrocardiogram, and since it was considered that these changes might be mediated through the autonomic nervous system, a ganglionic blocking agent, hexamethonium, was given to determine whether it might alter the responses.[6]

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METHODS AND PROCEDURE

Eleven patients with hypertensive cardiovascular and/or coronary artery disease with angina pectoris were selected for the study. During a two-step exercise tolerance test, all patients developed typical anginal complaints which were associated with electrocardiographic evidence of myocardial ischemia. Standard limb Leads I and II, and a single unipolar precordial lead, V_4, of the electrocardiogram were usually recorded simultaneously with brachial arterial pressure and a Dock or modified Dock ballistocardiogram using a direct-writing Sanborn Poly-Viso. Eighteen insulin tolerance tests were performed on the eleven patients. In addition to the changes in blood glucose following intravenous injection of insulin, usually at a dosage level of 0.1 unit per kilogram body weight, changes in serum potassium and sodium were likewise determined at fifteen- to thirty-minute intervals for a period of two hours. The blood glucose determination was done by Nelson's modification of Somogyi's method.[7] Serum electrolytes were analyzed by an internal standard flame photometer. Since these patients had been under personal observation and treatment for many months, the emotional reactions of anxiety and apprehensiveness to the procedure were thought to be minimized. Hexamethonium was given in a dose such that it produced postural hypotension and abolition of the hypertensive overshoot of the brachial pressure pulse to the Valsalva maneuver.

RESULTS

The results are summarized in Table I.

Intravenous Insulin (Without Prior Injection of Hexamethonium).—Following intravenous insulin, the blood sugar fell in eleven patients from an average level of 81 mg. per cent to 38 mg. per cent, the range of the falls varying from 28 to 59 mg. per cent (Table I). With the reduction in blood glucose there was no appreciable change in serum sodium. However, the serum potassium decreased on the average 0.7 meq. per liter, the range of the falls being from 0.1 to 1.4 meq. per liter. Six of the eleven patients had a fall in the blood pressure, the average of the decreases being 46 mm. Hg in the systolic, and 23 mm. Hg in the diastolic pressures. With the exception of three patients, none had an appreciable increase in the heart rate. Seven of the eleven patients showed definite electrocardiographic changes, which usually paralleled the changes in the blood glucose and serum potassium, but were unlike the myocardial ischemic changes (S-T depression with T-wave inversion) observed during exercise. The most common change was a flattening and broadening of the T waves. A less frequent alteration was an inversion or an uprighting of the T waves. The four patients who showed no electrocardiographic changes had left ventricular hypertrophy. Three patients developed an arrhythmia. Two had frequent premature auricular contractions, while one had premature ventricular contractions with an episode of transient ventricular tachycardia.

In none of the eleven patients who had readily induced signs of coronary insufficiency during exercise did intravenous insulin produce angina pectoris. During the period of hypoglycemia the patients experienced flushing of the

TABLE I. THE EFFECTS OF INTRAVENOUS INSULIN WITH ANGINA PECTORIS

PATIENT AGE SEX	PROCEDURE	BLOOD GLUCOSE (MG. %)	SERUM SODIUM (meq./L.)	SERUM POTASSIUM (meq./L.)	ECG	BLOOD PRESSURE (MM. HG)	PULSE RATE (BEATS PER MIN.)	COMMENTS
J.B.	Control	87	146	4.8	M.D. and A.F.	140/90	70	
72 M	Insulin (13 u.)	33	147	4.0	Multifocal P.V.B. Vent. tachy.	140/80	76	Weak, warm, sweating
T.N.	Control	60	149	4.6	L.V.H. Occ. P.A.B.	240/140	70	
52 F	Insulin (10 u.)	27	150	3.2	No change	210/110	80	Warm, weak, sweating, palpitation
H.H.	Control	81	145	3.8	M.D.	140/80	64	
62 M	Insulin (8 u.)	33	142	3.6	No change	140/80	64	Drowsy, weak, cold, shaking, sweating
T.L.	Control	77	147	5.0	Normal	220/80	80	
69 F	Insulin (10 u.)	28	148	3.2	T in I inverted Freq. P.A.B. (bigeminy)	185/70	80	Sleepy, warm, hungry
A.A.	Control	66	148	3.6	L.V.H.	230/150	72	
41 M	Insulin (15 u.)	37	149	3.1	No change	230/150	74	Sweating
E.S. 61 F	Control	77	146	3.8	Normal	170/90	72	
	Insulin (8 u.)	27	147	2.9	T in I flattened and broadened T in II and V_4 inverted	170/90	72	Weak, warm, lightheaded, sweating
	Control	78	150	3.7	Normal	190/90	72	
	C_6 (6.25 mg.)	74	150	3.7	No change	130/70	72	
	Insulin (8 u.)	23	150	3.3	T in I and V_4 flattened and broadened T in II inverted	90/50	72	Drowsy, sweating

L.F. 59 F	Control	80	150	3.8	L.V.H.	260/120	60	
	Insulin (8 u.)	34	151	3.2	T in I inverted T in II decreased T in V_4 diphasic	160/70	60	Warm, sleepy, flushing, sweating
	Control	68	150	3.6	L.V.H.	190/130	60	
	C_6 (10 mg.)	75	150	3.5	No change	140/80	68	
	Insulin (8 u.)	42	150	3.3	T in I and V_4 upright	140/70	72	Hungry, drowsy, flushing, sweating, semicomatose
E.P. 61 F	Control	84	147	3.8	P.M.I., old	180/80	75	
	Insulin (9 u.)	35	149	3.2	T in I and V_4 inverted	180/80	70	Headache, dizziness, sweating
	Control	85	143	4.1	P.M.I., old	160/80	60	
	C_6 (6.25 mg.)	91	145	4.0	T in V_4 decreased	155/80	60	
	Insulin (9 u.)	37	143	3.4	T in I, II, and V_4 flattened and broadened	110/60	58	No symptoms
E.C.* 65 F	Control	134	150	4.2	L.V.H.	190/90	86	
	Insulin (8 u.)	75	150	3.7	T in I, II, and V_4 upright	170/80	72	Warm, sleepy
	Control	169	148	3.6	L.V.H.	190/95	80	
	C_6 (7.5 mg.)	168	148	3.7	No change	120/70	82	
	Insulin (8 u.)	85	148	3.4	No change	105/55	80	Drowsy, chilly, shivering
I.R. 43 M	Control	74	148	4.7	L.V.H.	220/150	68	
	Insulin (10 u.)	46	146	4.6	No change	270/140	72	Drowsy, sweating
	Control	91	146	5.0	L.V.H.	240/120	56	
	C_6 (50 mg.)	93	146	5.0	No change	140/80	60	Dryness of mouth
	Insulin (10 u.)	52	148	4.7	No change	140/80	60	Drowsy

TABLE I.—CONT'D

PATIENT AGE SEX	PROCEDURE	BLOOD GLUCOSE (MG. %)	SERUM SODIUM (meq./L.)	SERUM POTASSIUM (meq./L.)	ECG	BLOOD PRESSURE (MM. HG)	PULSE RATE (BEATS PER MIN.)	COMMENTS
	Control	75	146	4.1	Normal	160/90	72	
	Insulin (8 u.)	46	148	3.7	T in I, II, and V_4 flattened and broadened	140/80	70	Warm, flushed
	Control	77	149	4.6	Normal	190/110	70	
M.W.	C_6 (25 mg.)	82	149	4.4	No change	125/80	76	Dryness of mouth
57 F	Insulin (8 u.)	35	150	3.6	T in I, II, and V_4 flattened and broadened	90/60	86	Weak, drowsy, sweating
	Control	80	149	3.5	Normal	190/110	76	
	Insulin (16 u. and 20 u.)	29	149	2.2	T in I broadened T in II and V_4 flattened and broadened	120/80	88	Drowsy, sweating, vision blurred

u. = unit, C_6 = hexamethonium, M.D. = myocardial damage, A.F. = auricular fibrillation, P.V.B. = premature ventricular beats, Vent. tachy. = ventricular tachycardia, L.V.H. = left ventricular hypertrophy, P.A.B. = premature auricular beats, P.M.I. = posterior myocardial infarction, Occ. = occasional, and Freq. = frequent.

*Patient studied after light breakfast.

face, generalized warmth, sweating, weakness and sleepiness, and occasionally mild headache, dizziness, jitteriness, and hunger. One patient developed semi-coma.

Intravenous Insulin After Pretreatment With Hexamethonium.—In six patients the average maximum fall in the blood glucose and serum potassium, without pretreatment with intravenous hexamethonium, was 43 mg. per cent and 0.5 meq. per liter. Following the injection of hexamethonium, intravenous insulin produced a comparable reduction in blood glucose (49 mg. per cent) and serum potassium (0.5 meq. per liter). The blood glucose responses are summarized in Fig. 1 in four patients. The changes in blood pressure and pulse

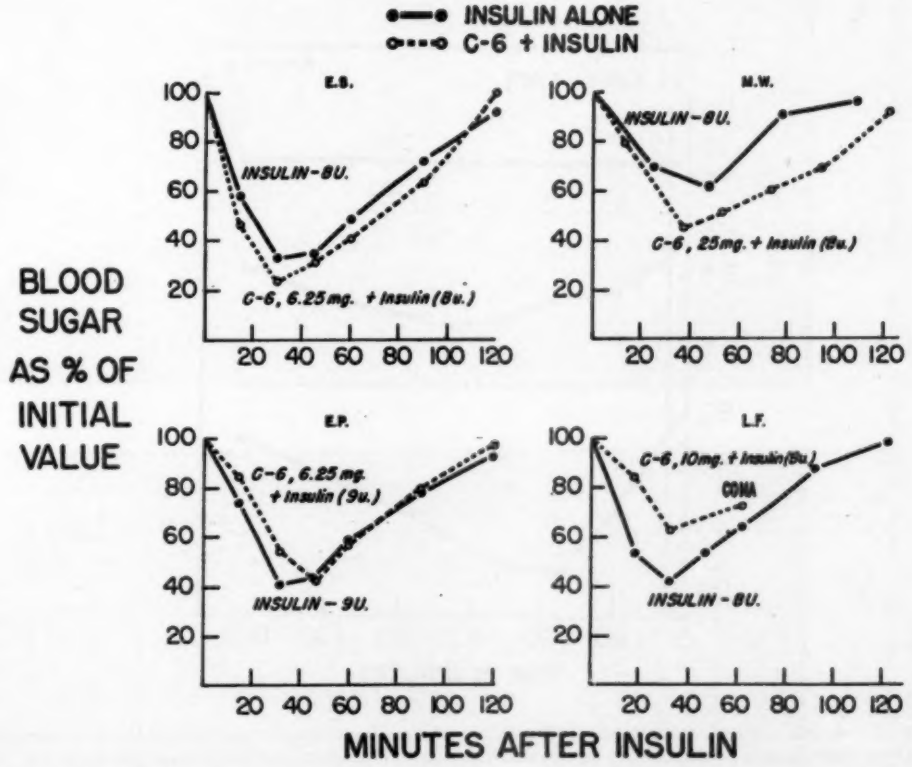

Fig. 1.—A chart showing the comparative blood glucose responses to intravenous insulin before and after pretreatment with hexamethonium (C_6) in four patients with coronary artery disease.

rate produced by intravenous insulin were similar both before and after pretreatment with hexamethonium. Likewise, similar electrocardiographic changes occurred both with and without pretreatment with hexamethonium, except in Patient E. C. The symptoms of hypoglycemia were not usually blocked by hexamethonium. However, in two patients (E.P., I.R.) pretreated with hexamethonium, sweating was absent after insulin.

Illustrative Responses to Intravenous Insulin.—Fig. 2 shows the typical electrolyte and blood sugar responses to intravenous insulin in a patient with angina pectoris. Within thirty to forty-five minutes after the injection of

insulin, the maximum fall in blood glucose occurred, and after two hours the blood sugar returned to its initial control level. The decreases in serum potassium paralleled those of the blood glucose while the serum sodium showed no essential change. The serum sodium, blood pressure, and pulse rate were unchanged.

Fig. 3 illustrates the chemical, circulatory, and electrocardiographic changes following intravenous insulin in a patient with angina pectoris. Although the blood sugar (glucose) fell from the initial value of 77 to 27 mg. per cent within forty-five minutes, the patient, like all other patients, did not develop chest pain. Paralleling these changes, the serum potassium fell from 3.8 to 2.9 meq. per liter, but the serum sodium, blood pressure, and pulse rate showed no change.

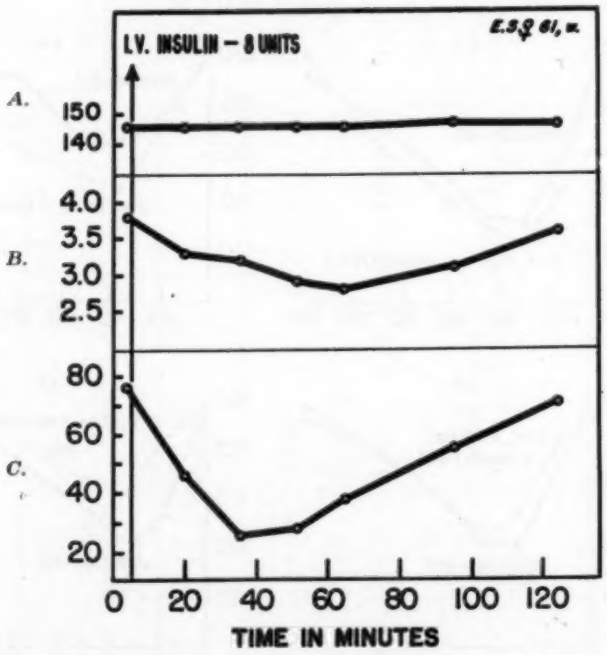

Fig. 2.—A chart showing the typical blood glucose and electrolyte responses to intravenous insulin in a patient with angina pectoris. *A*, serum sodium (meq./L.); *B*, serum potassium (meq./L.); *C*, blood glucose (mg. per cent).

At the maximum depression of the blood glucose and serum potassium the T wave in Lead I decreased, in Lead II inverted, and in V_4 became diphasic. After two hours with the return of the serum potassium and blood glucose to the initial levels, the electrocardiogram reverted to the type seen during the control period.

Fig. 4 illustrates the absence of electrocardiographic changes during insulin-induced hypoglycemia in a patient (H.H.) with angina pectoris. The blood glucose fell from the initial value of 81 to 33 mg. per cent within thirty minutes, but no appreciable change in the serum potassium occurred. Likewise, there was no change in the electrocardiogram or ballistocardiogram.

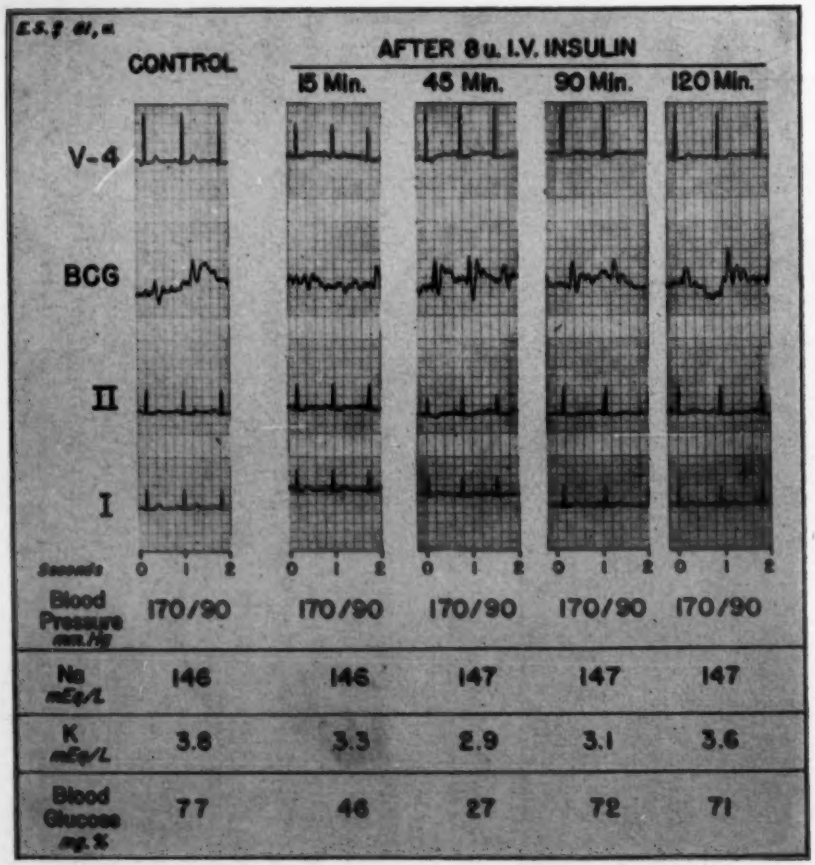

Fig. 3.

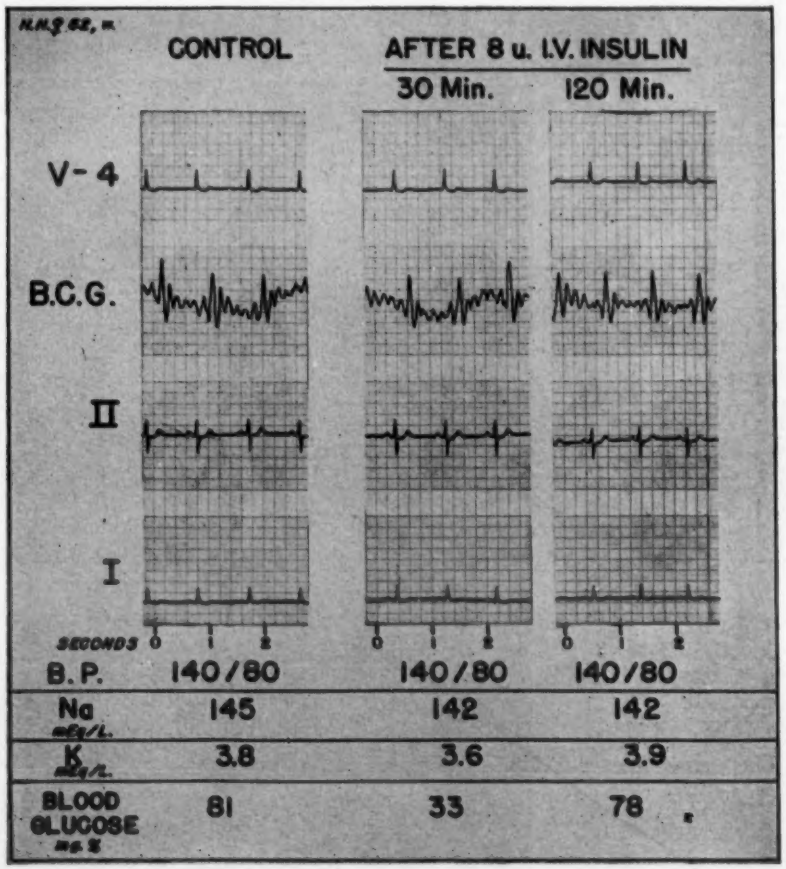

Fig. 4.

Fig. 3.—The effects of insulin-induced hypoglycemia in a patient with angina pectoris. The changes in the electrocardiogram after intravenous insulin paralleled the changes of blood glucose and serum potassium.

Fig. 4.—This figure shows the absence of electrocardiographic changes during insulin-induced hypoglycemia in a patient with angina pectoris, which were associated with no appreciable changes in the serum potassium.

Fig. 5 shows the failure of repeated doses of intravenous insulin to produce anginal pain in a patient (M.W.) with status anginosus. The patient suffered from intractable angina and complicating shoulder-hand syndrome, the latter being treated with intermittent stellate ganglionic block. Although insulin shock was induced for a period of at least two hours, the patient did not develop an attack of angina pectoris. During the hypoglycemic state there was a re-

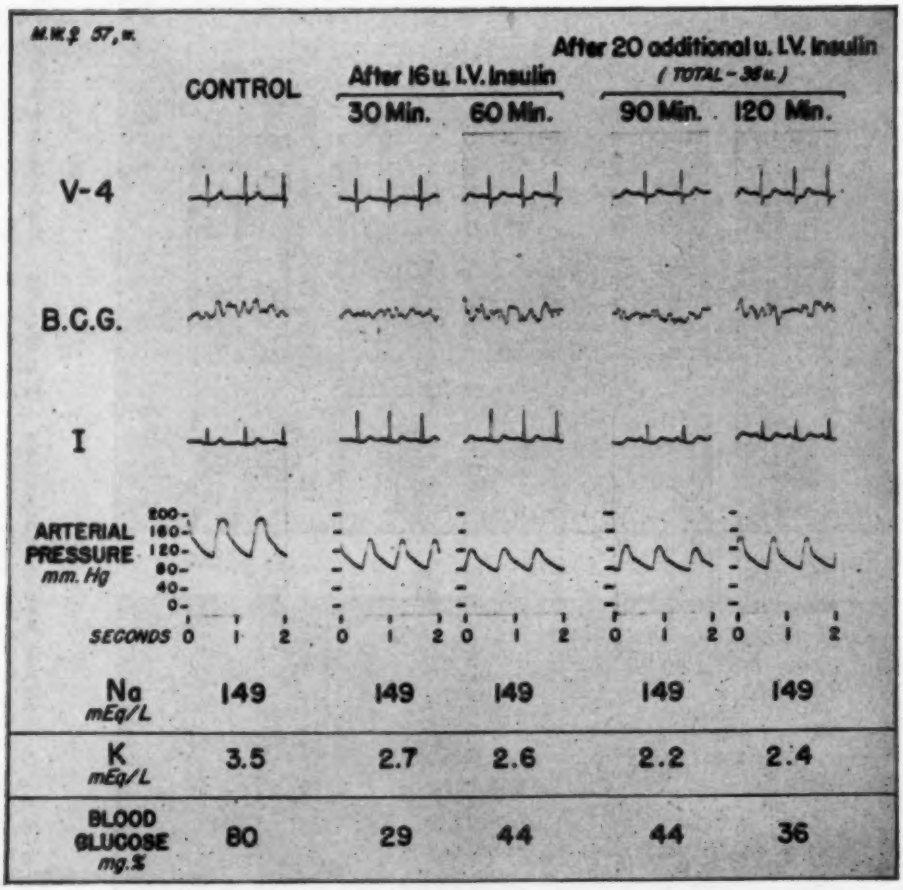

Fig. 5.—This figure shows the failure of marked and prolonged hypoglycemia to produce anginal pain and coronary insufficiency in a patient with status anginosus.

duction in blood pressure, but no change in the pulse rate. The accompanying changes in the electrocardiogram (broadening and flattening of T waves in Leads I and V_4) were associated with an appreciable decrease in the serum potassium and blood glucose and were unlike the ischemic changes produced by the exercise tolerance test.

A ganglionic blocking agent, hexamethonium, was given to patient E.S. in an attempt to prevent electrocardiographic changes (Fig. 6) which appeared during insulin-induced hypoglycemia in the previous study (see Fig. 2). Hexamethonium produced a noticeable fall in the blood pressure, but no changes in serum electrolytes, blood glucose, the electrocardiogram, or the ballistocardi-

ogram. During hypoglycemia the electrocardiographic changes were not blocked by hexamethonium but were similar to those shown in Fig. 2. The fall in blood glucose was similar, but the reduction in serum potassium was less. Although the blood pressure remained reduced in this study for at least two hours, the electrocardiogram returned toward the control pattern with the recovery of the serum potassium and blood glucose concentrations.

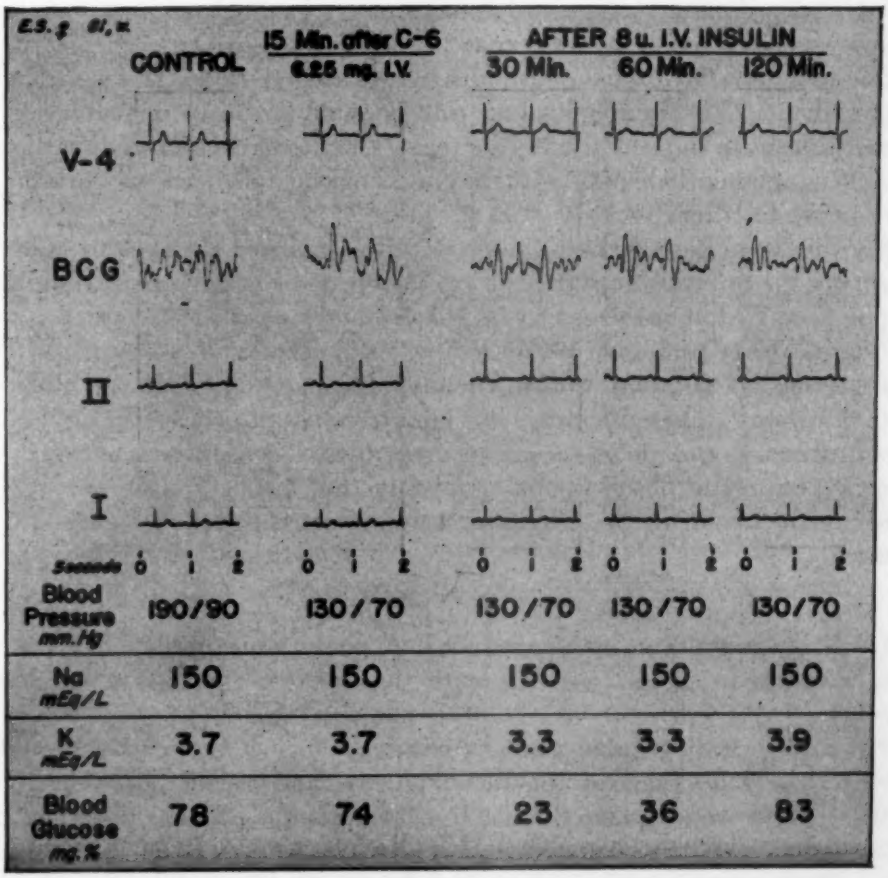

Fig. 6.—This figure shows the inability of hexamethonium to block changes in the electrocardiogram produced by intravenous insulin.

DISCUSSION

The group of eleven patients did not develop angina pectoris during eighteen episodes of experimentally-induced insulin hypoglycemia. Included in the group was one patient who was maintained in insulin shock for over two hours and another who had developed semicoma and required intravenous glucose therapy. However, the group frequently developed electrocardiographic alterations during the hypoglycemic state, which were not dissimilar to those reported in normal subjects.[1] The electrocardiographic changes consisted of

broadening, flattening, and inversion of the T waves and disturbances in rhythm such as premature beats, bigeminy, and ventricular tachycardia. These abnormalities were associated with decreases in the blood glucose and serum potassium; indeed, the changes in T waves were often not unlike those observed during other hypopotassemic states. It is unlikely that the electrocardiographic changes were caused by coronary insufficiency, since they were totally unlike those observed during a documented attack of angina pectoris. The absence of chest pain during the hypoglycemic state is added evidence that the changes in the electrocardiogram were not due to coronary insufficiency. No convincing evidence was obtained to suggest that the alterations in the electrocardiogram were due to sympathoadrenal neural discharges secondary to the insulin-induced hypoglycemia. The findings against this possible pathway of mediation were that the pulse rate did not usually increase, the blood pressure fell rather than rose, and ganglionic blockade with hexamethonium failed to prevent the electrocardiographic alterations.

The failure to induce angina pectoris with insulin in the present study does not support the impression that coronary insufficiency is a frequent complication of hypoglycemia, but rather suggests that this complication is rare. In evaluating the incidence of angina pectoris during hypoglycemia, a number of factors should be considered in addition to the magnitude of the fall in the blood sugar and its duration. These include emotional responses to the procedure, changes in blood pressure and pulse rate, and disturbances in cardiac rhythm. From present experimental observations it appears that hypoglycemia per se is not necessarily the cause for the angina pectoris reported to follow excessive insulin treatment.

CONCLUSIONS

1. Experimentally, insulin-induced hypoglycemia failed to precipitate angina pectoris in eleven patients with documented attacks of coronary insufficiency.
2. Electrocardiographic changes occurred during hypoglycemia and were related to the reductions in the blood glucose and serum potassium concentrations. They were unlike the electrocardiographic changes observed during exercise-induced angina pectoris.
3. Pretreatment with intravenous hexamethonium did not consistently alter symptoms or the response of the blood glucose, serum electrolytes, and the electrocardiogram to intravenous insulin.
4. The experimental observations suggest that the dangers from insulin-induced hypoglycemia in patients with coronary artery disease may, on occasion, have been overemphasized.

SUMMARIO IN INTERLINGUA

Le studio esseva interprendite pro evalutar le effectos cardiovascular de hypoglycemia inducite per insulina in patientes con documentate angina de pectore. In 11 patientes con insufficientia coronari, le administration intravenose de insulina in doses de inter 8 e 36 unitates produceva un reduction del

sucro sanguinee ab un nivello median de 81 mg pro cento a un nivello median de 38 mg pro cento. Tamen, nulle del patientes disveloppava angina de pectore, includente illes qui disveloppava choc insulinic e semicoma. Del altere latere, la electrocardiogrammas (I, II, III, e V_4) monstrava frequente alterationes del unda T e sporadic arrhythmias que esseva relationate a reductiones del glucosa sanguinee e del kalium seral e non a alterationes del pression brachio-arterial e del frequentia pusatile. Le responsas a insulina non esseva uniformemente alterate per hexamethonium intravenose.

Le observationes experimental indica que hypoglycemia per se non es capace a causar angina e que le periculo de hypoglycemia inducite per insulina ha possibilemente essite exaggerate.

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THE SIGNIFICANCE OF THE PULMONARY VASCULAR BED IN CONGENITAL HEART DISEASE

III. Defects Between the Ventricles or Great Vessels in Which Both Increased Pressure and Blood Flow May Act Upon the Lungs and in Which There Is a Common Ejectile Force

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IN THE preceding paper we have dealt with the normal evolutionary pattern followed by the pulmonary vascular bed from fetal to adult life, and we have discussed changes in the pulmonary vascular bed found in patients who had an anatomic pulmonary stenosis. In the present section we will consider alterations in the pulmonary vascular bed which occur when the lungs are exposed to systemic pressure. However, before discussing the results obtained from microscopic examination of the lungs of such cases it is necessary to consider certain concepts which aid in the interpretation of the clinical data and their relationship to lumen:wall ratios.

When the cross-sectional area of a ventricular septal defect approximates that of the aortic orifice, the systolic pressure generated in each ventricle must be the same. In Edward's terminology, a "systemic right ventricle" or "common ejectile force" is present.[1-4] Systolic pressures in the aorta and pulmonary artery being equal, distribution of blood into the two circulations will be dependent upon their respective peripheral vascular resistances. The hemodynamic expression of peripheral resistance is diastolic pressure. Consequently, since the peripheral vascular resistances in the two circulations, respectively, are not identical, diastolic pressures are unequal. Mean arterial pressure in the pulmonary and systemic circulations will vary proportionately to changes in the diastolic pressure.

It must be emphasized that all patients with a common ejectile force have pulmonary hypertension of systemic magnitude during the entire course of their life. Therefore, the clinical picture presented by such a patient is not dependent upon the mere presence of pulmonary hypertension, but upon the relative blood flow through the two circulations. Blood flow in turn is controlled by the resistance offered by the peripheral arterial bed. Systemic vascular resistance

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is relatively static. On the other hand, pulmonary vascular resistance is not at all static, but varies during postnatal life according to the evolutionary pattern followed by the small pulmonary arteries.

Theoretically, there are three possible courses that the pulmonary vascular bed may follow after birth in the presence of a common ejectile force.[12,13] These result in three distinctly different clinical syndromes or phases:

Phase I.—Pulmonary vascular evolution follows a relatively normal course with falling peripheral vascular resistance in the pulmonary vascular bed. Consequently, a progressively larger proportion of the cardiac output passes to the lungs and a relatively smaller quantity of blood to the body. In order to maintain an adequate systemic blood flow, cardiac output must rise. High output failure frequently ensues. The clinical picture is that of an underdeveloped, thin child with a large heart, excessive blood flow to the lungs, and high-output cardiac failure (Fig. 1*A*).

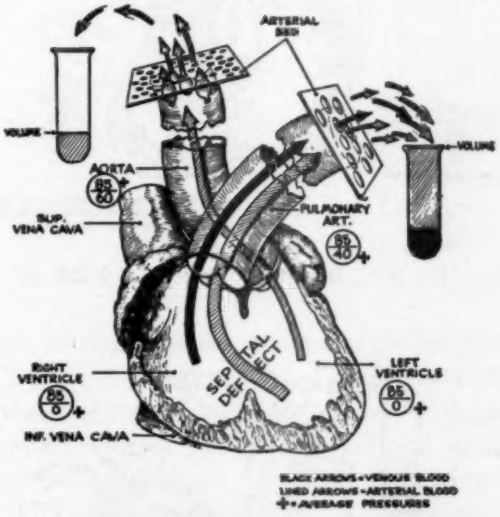


Fig. 1*A*.—Illustrated diagram of Phase I.

Phase II.—Fetal state, thick-walled, small-lumened vessels and high pulmonary vascular resistance continues with approximately equal peripheral resistances in the two circulations. Thus, blood flows will be similar and a state of circulatory balance will exist, allowing normal growth and development. The patient may be symptom-free, cyanosis is minimal or absent, and no significant cardiac enlargement occurs (Fig. 1*B*).

Phase III.—Pulmonary vascular resistance increases gradually with the development of secondary intimal changes and eventually exceeds the systemic resistance. More blood goes to the body than to the lungs. Growth and development are retarded due to anoxia. Dyspnea and cyanosis are present. (Fig. 1*C*).

During the progression from Phase I to Phase III the pulmonary blood flow decreases markedly, but the systemic output increases only slightly. Systolic pressure rises only slightly. Consequently, the total work of the heart is de-

creased and this accounts for the decrease in heart size and the establishment of cardiac compensation.

In each of the three phases the underlying cardiac malformation may or may not be the same. The patient may have a large ventricular defect, single ventricle, true truncus arteriosus, large patent ductus arteriosus, or aortic septal

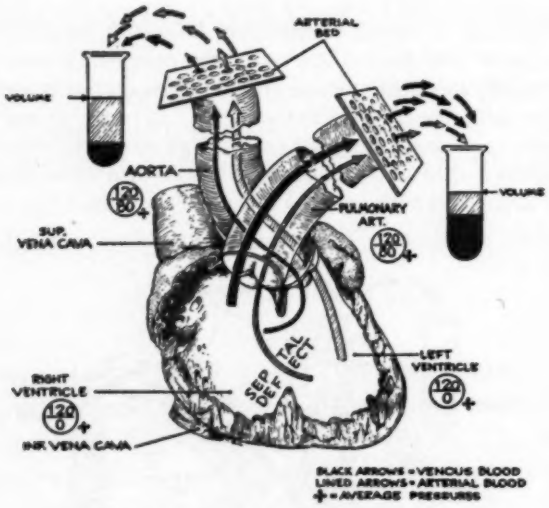


Fig 1*B*. · Illustrated diagram of Phase II.

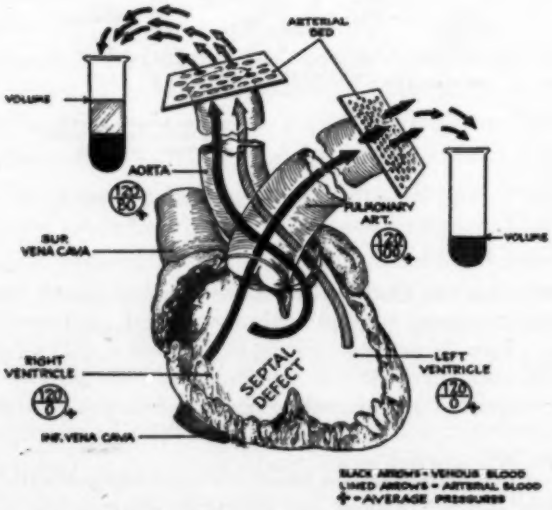


Fig. 1*C*.—Illustrated diagram of Phase III.

defect. The common denominator in all phases, no matter what form of malformation exists within the heart, is the presence of a common systolic pressure in both right and left ventricle, pulmonary artery, and aorta (Table I).

TABLE I

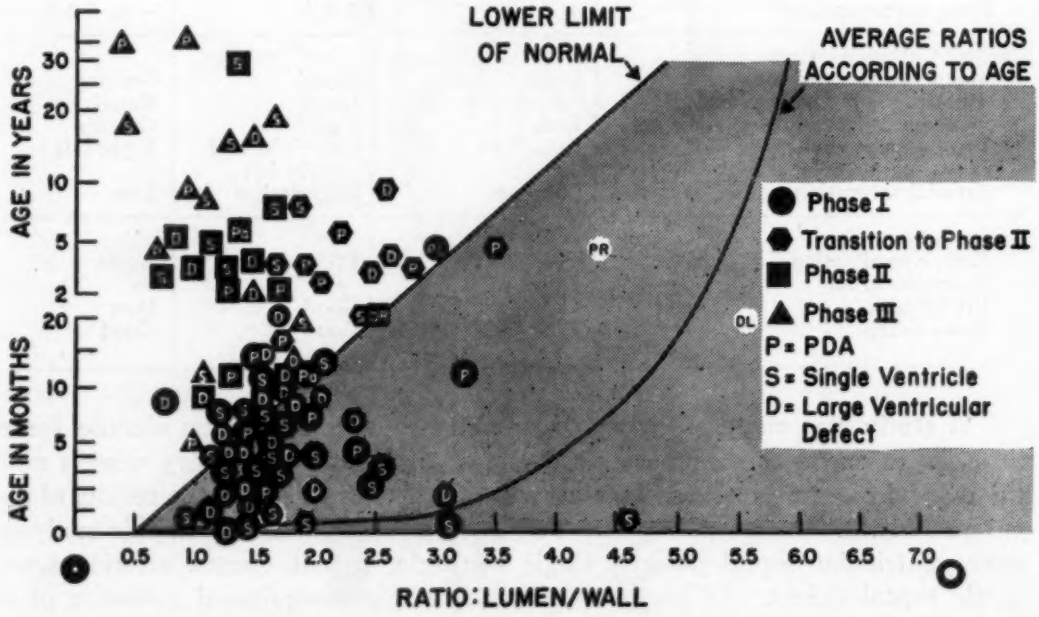
PHASES	I	II	III
Clinical			
Growth	Retarded	Normal	Retarded
Infections	Pulmonary	No	Chronic Pulmonary
Dyspnea	++++	±	++
Cyanosis	No	±	++++
Cardiac failure	++++	No	±
Pulmonary edema	++++	No	No
Radiologic			
Cardiac enlargement	++++	+	+
Specific chamber enlarged	Left auricle	±	No
Lung fields vascular	++++	+++	− to +++
Cardiac Catheterization			
Mean PA pressure to aorta	Less	Equal	Greater
Systolic PA pressure to aorta	Equal	Equal	Equal
Diastolic PA pressure to aorta	Less	Equal	Greater
Predominant shunt	Left-right	Left-right and right-left	Right-left
Arterial saturation	Normal	Slightly low	Low
Angiocardiography			
Early visualization	PA	PA and aorta	Aorta
Reopacification	PA	—	—
PA filling	Good	Good	Poor
Aorta filling	Poor	Good	Good

A study was made of eighty-seven patients with a common ejectile force in order to correlate the anatomic changes within the pulmonary vessels and the clinical picture presented by the patient. Graph I depicts the results of an analysis of the lumen:wall ratios. The malformations included in this analysis were ventricular septal defects, single ventricle, patent ductus arteriosus, or aortic septal defect. In each instance there was unequivocal evidence of a common ejectile force. In some the anatomic malformation itself was sufficient proof; i.e., single ventricle without pulmonary stenosis, ventricular defect with clearcut overriding of the aorta, aortic septal defect equal in size to the aortic valve, or defects in which both great vessels arise from the same ventricle. In the others identical systolic pressures were recorded from the pulmonary artery and aorta. Each case was allocated to the appropriate phase on the basis of clinical and laboratory data independently of the results of the microscopic examination of the lungs. A circle was used to designate Phase I; a square, Phase II; a triangle, Phase III; and a hexagon represents a transition between Phases I and II.

The lumen:wall ratio of these patients deviates strikingly from the normal. This deviation follows a definite pattern. Patients presenting the clinical picture of high output cardiac failure (Phase I) tended to be young and had ratios somewhat lower than normal patients of the same age but greater than the newborn. Patients with a balanced circulation (Phase II) ranged in age from 6 months to 20 years and had definitely reduced ratios. Cyanotic patients

in clinical Phase III were older and had ratios markedly below those of normal patients of their own age.

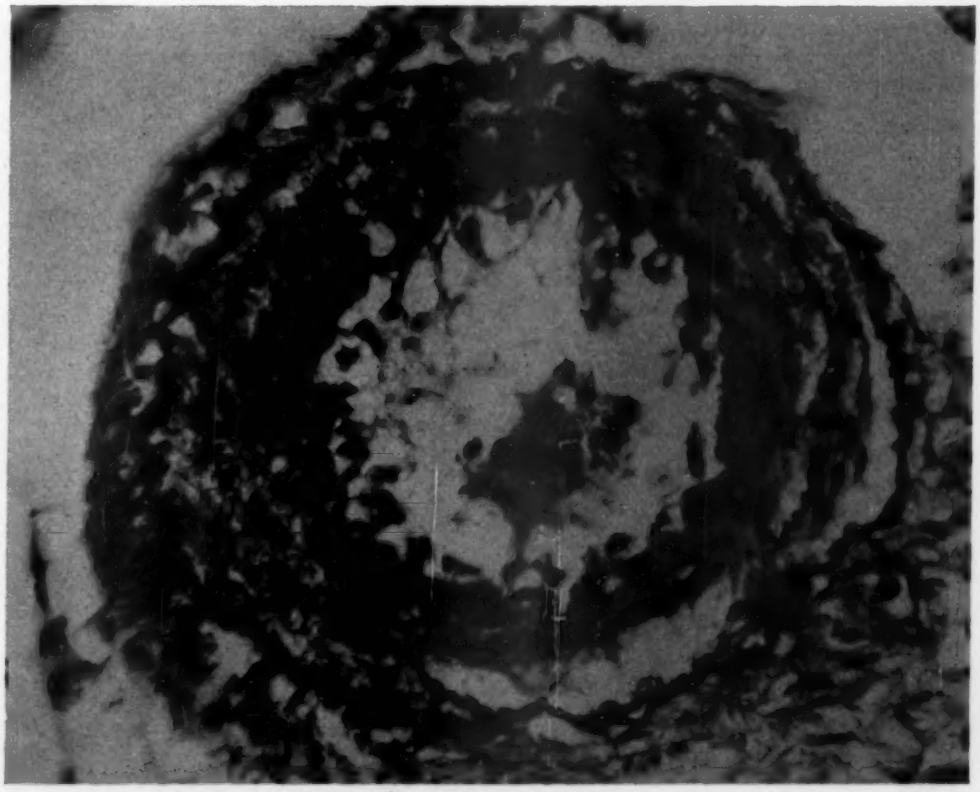
The typical vascular progression, then, is for a small pulmonary artery, narrow at birth, to become somewhat larger-lumened and thinner-walled during the first weeks of life. Following this, there is a gradual shift back toward the thick-walled, small-lumened status. Eventually, if the patient survives long enough, vessels have thicker walls and smaller lumens than those found at birth. While this is the usual course, it is also possible for vessels which are normal at birth to show only progressive hypertrophy without ever passing through a phase of relatively wide lumens and thin walls.



Graph I.—Graph illustrating the lumen:wall ratios obtained from eighty-seven patients with a common ejectile force. The letters *DL* and *DR* indicate the ratios obtained from the left and right lungs, respectively, of a 20-month-old infant with Eisenmenger's complex and a single pulmonary artery to the right lung. The letters *PR* and *PL* indicate the ratios obtained from a 4-year-old patient with tricuspid atresia, a Potts-Smith anastomosis directing additional blood flow to the left lung only.

There is a clear correlation between the progression of vascular changes and the clinical signs and symptoms observed in patients in whom a malformation with a common ejectile force exists. The patient appears normal at birth and for a short time thereafter. As pulmonary vascular evolution results in a falling pulmonary resistance, blood flow to the lungs gradually increases and the early signs of cardiac embarrassment, slow weight-gain, and rapid respirations, become manifest. Gradual enlargement of the heart occurs. Pneumonia is frequent. Finally, high-output cardiac failure ensues with pulmonary congestion and enlargement of the liver. Many of these infants die in spite of extensive medical therapy. This syndrome represents Phase I (Fig. 1*A*). Microscopic

examination of the lungs reveals extensive congestive changes with edema of the alveolar walls and the presence of fluid and heart failure cells within the alveoli. Areas of hemorrhage may be found. The larger pulmonary vessels show evidence of medial hypertrophy. The small muscular pulmonary arteries used in the determination of the lumen:wall ratios show thickening of the media, but rarely is any intimal proliferation found (Fig. 2*A*). The adventitia in the young infant may be abundant. Capillaries are dilated and filled with blood cells. Veins appear abnormally large, but in most instances there is no thickening of the wall.



Figs. 2*A* to *D*.—Photomicrographs of small pulmonary arteries illustrating the three phases.
Fig. 2*A*.—Phase I. From a 3-month-old child with a large ventricular defect and congestive cardiac failure.

Patients who survive Phase I pass into Phase II. One reason for survival is the ability of the heart to hypertrophy sufficiently to carry the increased work load. A second reason for survival may be a relative change in the size of the defect as compared to the size of the aortic orifice. If the left heart and aortic valve increase in size more rapidly than the defect, a point may be reached where the defect itself limits the volume of blood flow which passes through to the lungs. Therefore, a pressure gradient appears between the left and right ventricle and the course of such a patient no longer is that of a common ejectile force. This developmental course will be discussed in greater detail in a subse-

quent section. A third reason, perhaps the most important, is that normal pulmonary vascular evolution does not continue. The small arteries regain their thick walls and small lumens and show an absolute increase in muscular thickness and in elastic tissue of the media. No evidence of congestive failure is found in the lungs. Alveoli are normal in appearance. Capillaries are not congested and veins are normal in size (Fig. 2*B*). Thus, a high pulmonary vascular resistance is regained and the blood flow to the two circulations is brought within reasonable limits (Fig. 1*B*). The clinical status of the patient is improved and his good condition lulls the physician and the family into a false feeling of security and hopes for a bright future.

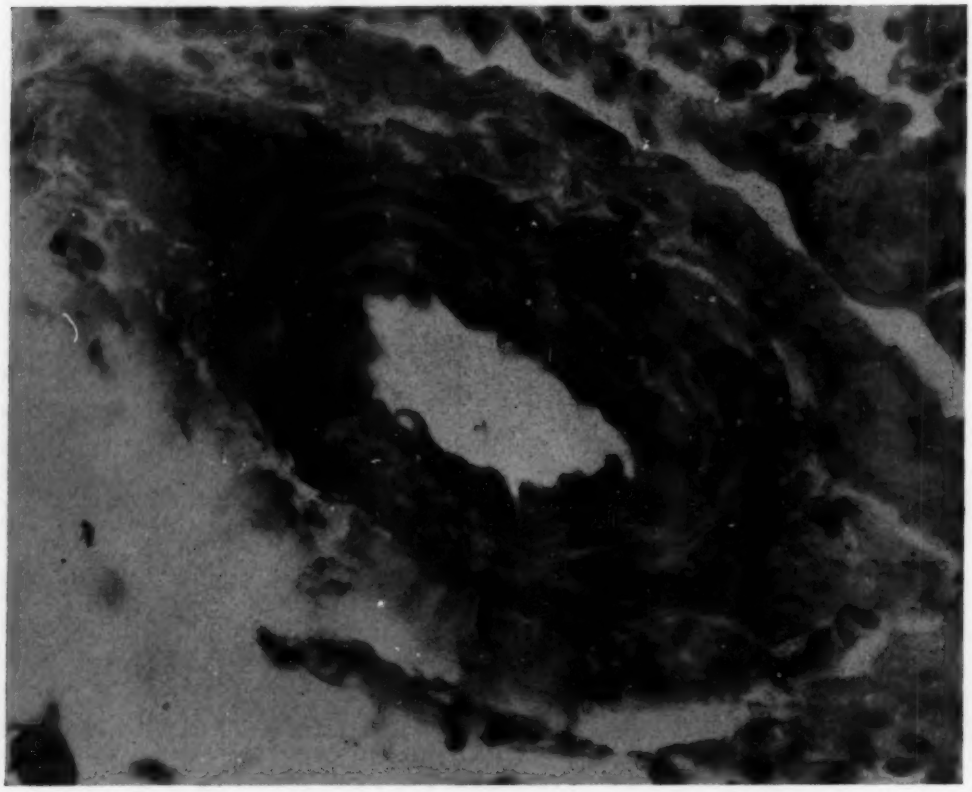


Fig. 2*B*.—Phase II. From a 2½-year-old girl with a large ventricular defect and no evidence of cardiac failure.

For reasons that appear to be related to the presence of a systemic pressure in the pulmonary artery[14-19] pulmonary resistance does not remain balanced but continues to increase. Further medial hypertrophy takes place in the small pulmonary arteries and, in addition, intimal thickening is noted. Pulmonary resistance eventually becomes greater than systemic resistance. Consequently, it now becomes easier for the heart to pump blood into the body than the lungs and the patient becomes cyanotic. This represents Phase III (Fig. 1*C*). The characteristic microscopic appearance of the lungs is that of extensive medial

hypertrophy and intimal proliferation of the walls of the pulmonary vessels, so that in some the lumen is almost obliterated (Fig. 2*C*). Both large and small pulmonary arteries are affected. In contrast, some of the small pulmonary arteries appear quite normal. However, the reason for this becomes clear when serial sections are examined closely, for a point of almost complete obstruction may be found where a small muscular artery branches. At the site of branching the intima gives a heaped-up appearance and the lumen into the daughter vessel is slitlike. Distal to this point of obstruction the pulmonary vessels may be thinned out and may appear perfectly normal.

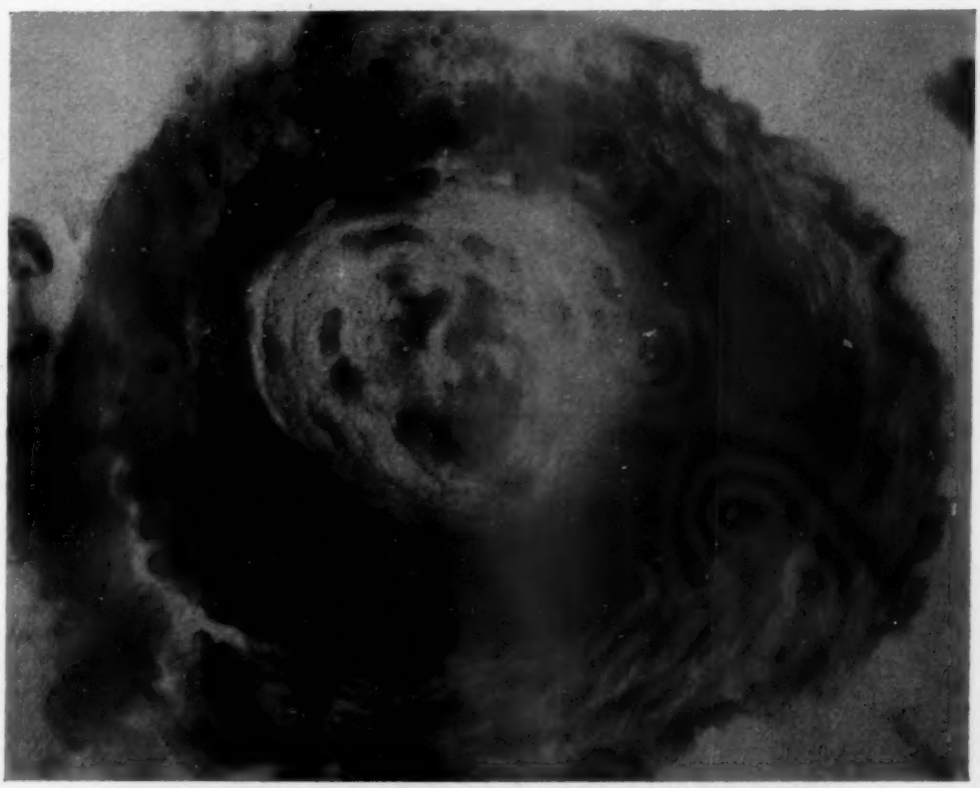


Fig. 2*C*.—Phase III. From a 7-year-old boy with a large ventricular defect, coarctation of the aorta, cyanosis, a small heart, and no failure.

In older patients who are in Phase III a different picture may present itself. This picture is characterized by large hypertrophied arteries in which there has been destruction of the elastica interna and externa and massive proliferation of the intima. Recanalized areas are present within the lumen. In addition to this there are endothelialized spaces, lying in the adventitia and media and in the perivascular space, which appear to be vascular lakes (Fig. 2*D*). The etiology of this particular lesion has been open to question. Such lesions are seen as the end result of a longstanding thrombotic[20] process. Some authors have suggested these lesions represent congenital arteriovenous[15,25] fistulae, but

serial sections fail to show any direct connection between the pulmonary veins and the involved artery. However, similar lesions have been produced experimentally in dogs by the production of acute pulmonary hypertension.[16,19] The pathogenesis of the experimental lesion appears to be an acute arteritis resulting from trauma to the wall of the vessel, rupture, perivascular and intravascular hemorrhage, and subsequent scarring. It seems reasonable to assume that the changes found in patients with a common ejectile force who have been in Phase III for a long period of time represent the end result of trauma to the pulmonary vessels from the elevated pulmonary pressure.

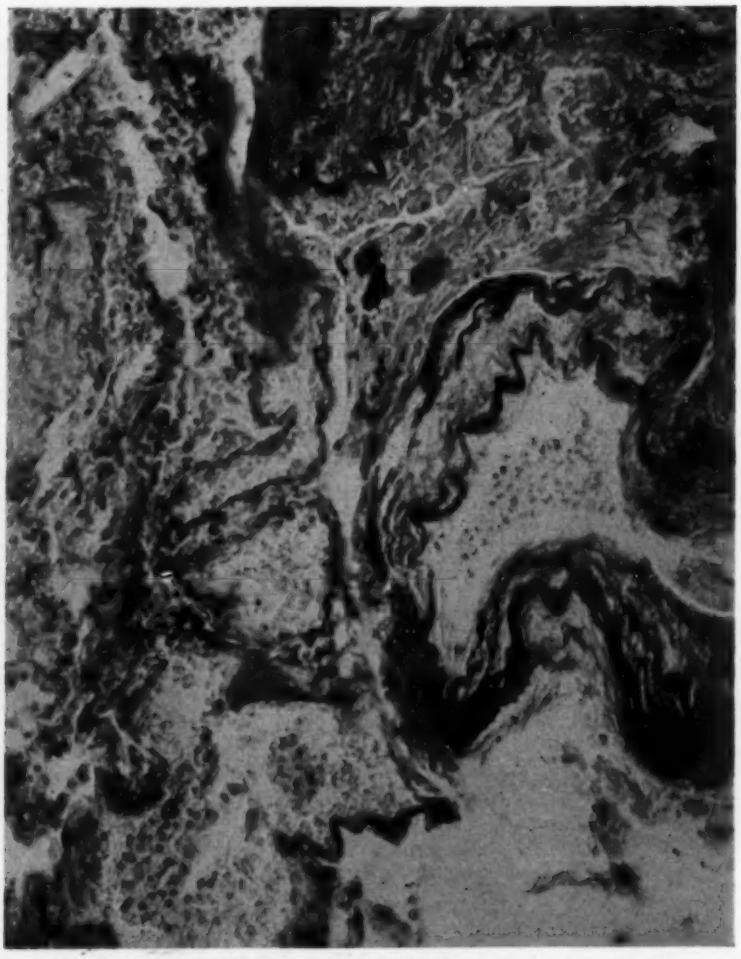
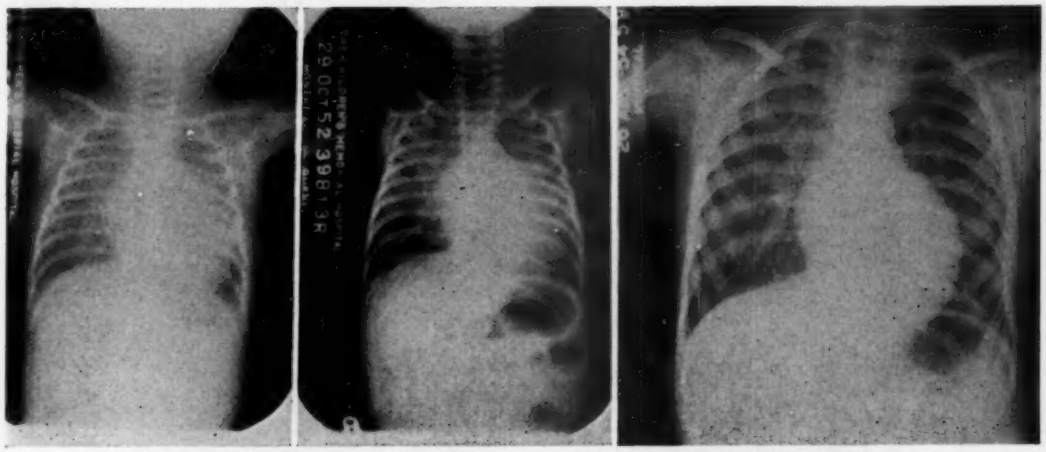


Fig. 2*D*.—Phase III. From a 36-year-old woman with a reverse patent ductus arteriosus, cyanosis, and no cardiac failure.

The progression of characteristic clinical findings from birth to Phase III can best be illustrated by citing several typical case histories.

CASE 1.—C.L. This infant was considered to be perfectly well until the sudden onset of respiratory distress at 5 weeks of age. He entered the hospital in severe congestive failure with dyspnea, cyanosis, evidence of pulmonary congestion, cardiac enlargement, an enlarged liver, and peripheral edema. No murmurs were present. The electrocardiogram revealed evi-

dence of left ventricular hypertrophy. The P waves were tall and peaked. Response to digitalis and other medical measures was only fair. He remained in a critical condition for about six weeks and then gradually began to improve. Weight-gain was slow but steady. At 5 months



A. *B.* *C.*

Fig. 3.—X-rays of the chest taken of C.L. at 5 weeks (*A*), 8 weeks (*B*), and 20 months (*C*) of age, respectively. Note the progressive decrease in heart size and clearing of the pulmonary vascular markings.

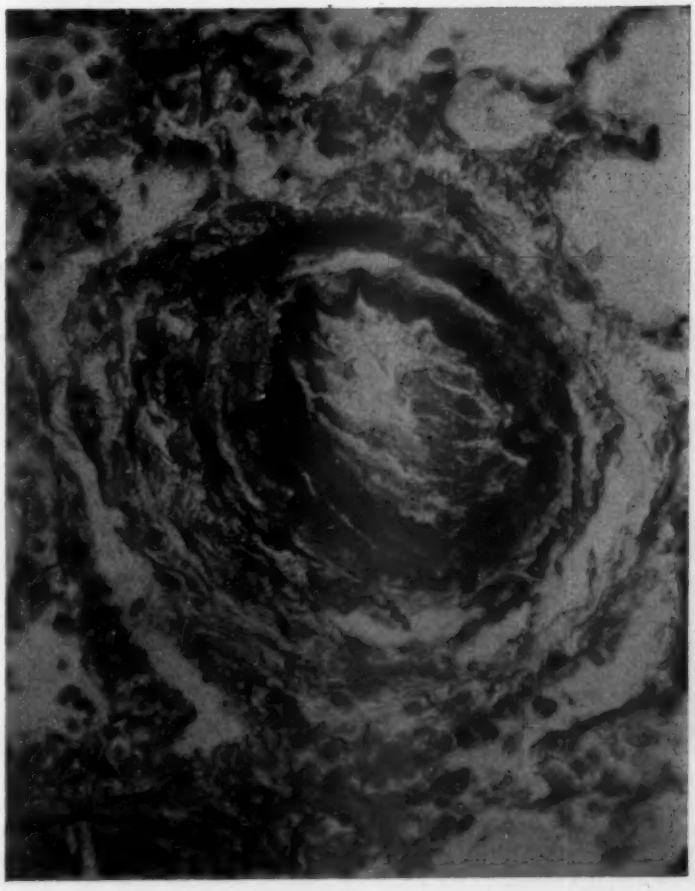


Fig. 4.—Photomicrograph of a small muscular pulmonary artery obtained from Case 1 (C.L.). Note the accentuation of the elastica interna and externa and the presence of intimal proliferation.

of age there was no evidence of cardiac failure, and at about 1 year of age digitalis was discontinued. Cyanosis, present in the initial episode of acute failure was slight after his condition improved, and then became increasingly pronounced. There was a gradual decrease in heart size (Fig. 3). At 20 months of age he died of measles encephalitis. Autopsy revealed the presence of a single ventricle with a transposition of the great vessels and complete interruption of the arch of the

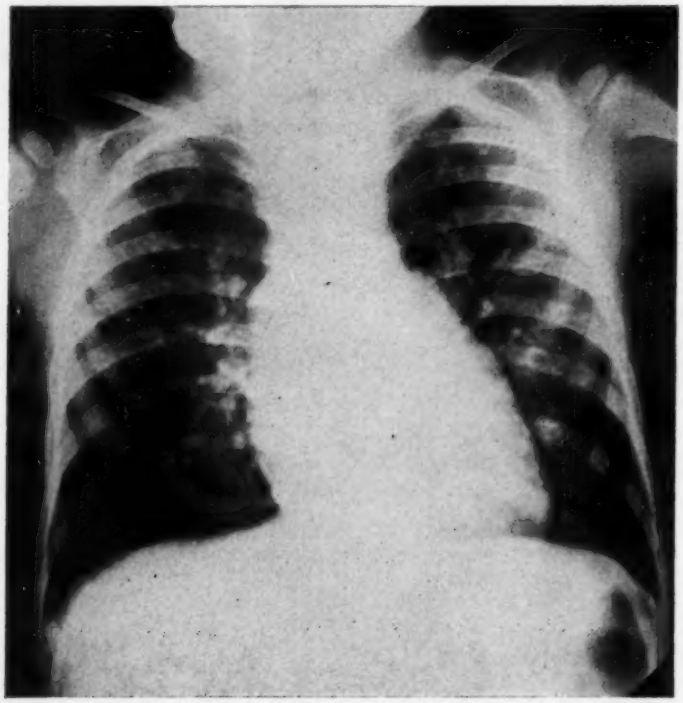
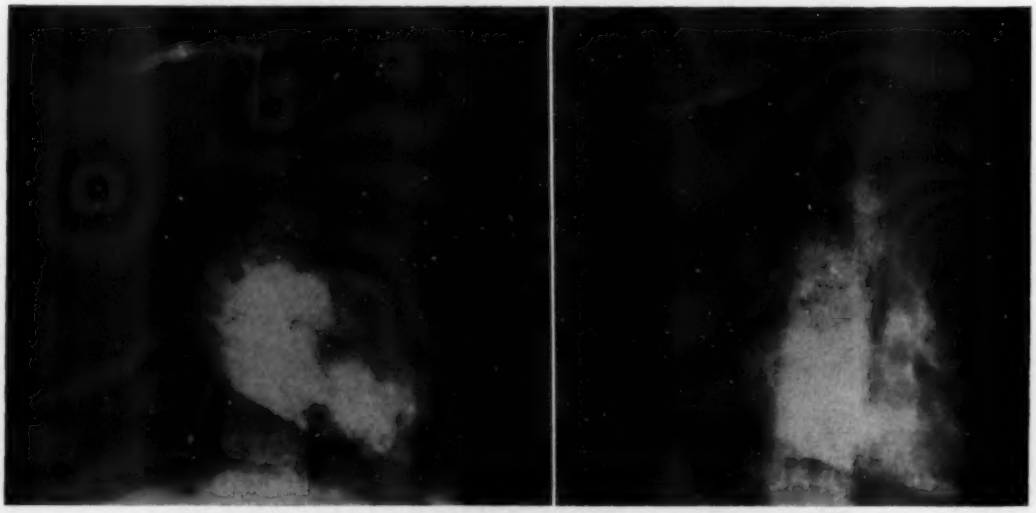


Fig. 5.—X-ray of the chest of C.W.C. demonstrating the essentially normal size of the heart and normal-appearing pulmonary vascular markings.



A. *B.*

Fig. 6.—Angiocardiogram of C.W.C. demonstrating filling of a common ventricle in the first film (*A*) and filling of a rudimentary outlet chamber in the second film (*B*). The aorta appears to arise from the rudimentary outlet chamber, the pulmonary artery from the common ventricle.

aorta. The distal aorta received blood through a large patent ductus arteriosus. Microscopic examination of the lung revealed marked hypertrophy of the media of the small muscular pulmonary arteries. The lumen:wall ratio was 1.9 (Fig. 4).

CASE 2.—C.W.C. This 7-year-old boy was first noted to be cyanotic within a few weeks after birth. Examination at that time revealed the presence of a systolic murmur. The second heart sound at the base was not split. X-rays revealed a small heart and normal pulmonary vascular markings. He was followed closely for a period of five years without significant change in clinical and radiologic findings (Fig. 5). During this period cyanosis and exertional dyspnea continued. The patient was subject to repeated throat and ear infections, but pulmonary in-

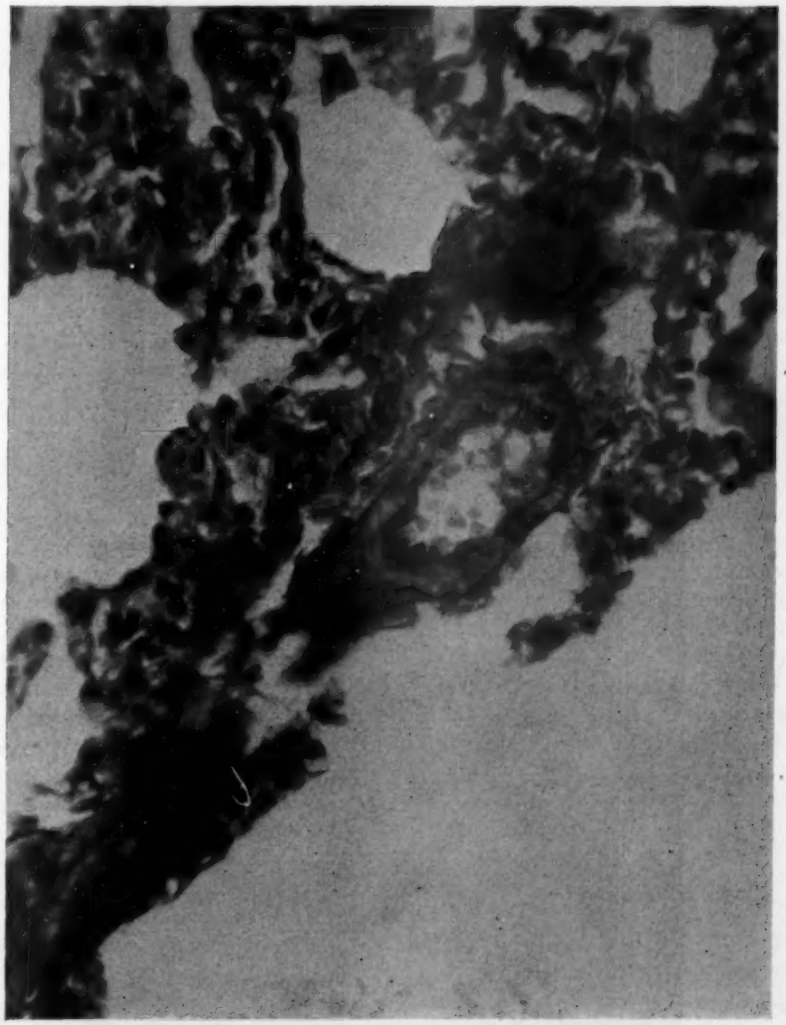


Fig. 7.—Photomicrograph of a small pulmonary artery from C.W.C. Note the thick media and absence of intimal proliferation.

fections did not occur. Angiocardiography and cardiac catheterization established the diagnosis of a single ventricle with transposition of the great vessels. The aorta arose anteriorly and to the left from a rudimentary outlet chamber. The pulmonary artery arose posteriorly from the main ventricular chamber (Fig. 6). Unfortunately, the pulmonary artery could not be catheterized, so that a pulmonary arterial pressure was not obtained. It was decided on the basis of the history and physical examination that the patient had, in addition to a single ventricle and

transposition of the great vessels, a pulmonary stenosis. Surgery was advised. Upon opening the chest, a tense pulmonary artery was found. Systolic and diastolic pressures obtained from the aorta and pulmonary artery were identical. Consequently, a shunt procedure was not done. Instead, the main pulmonary artery was narrowed about 70 per cent to the point where there was a moderate decrease in the distal pulmonary artery pressure.[10,26-28] After a stormy immediate postoperative course, the patient improved. Sufficient time has not elapsed to assess whether the patient has been permanently improved or not.

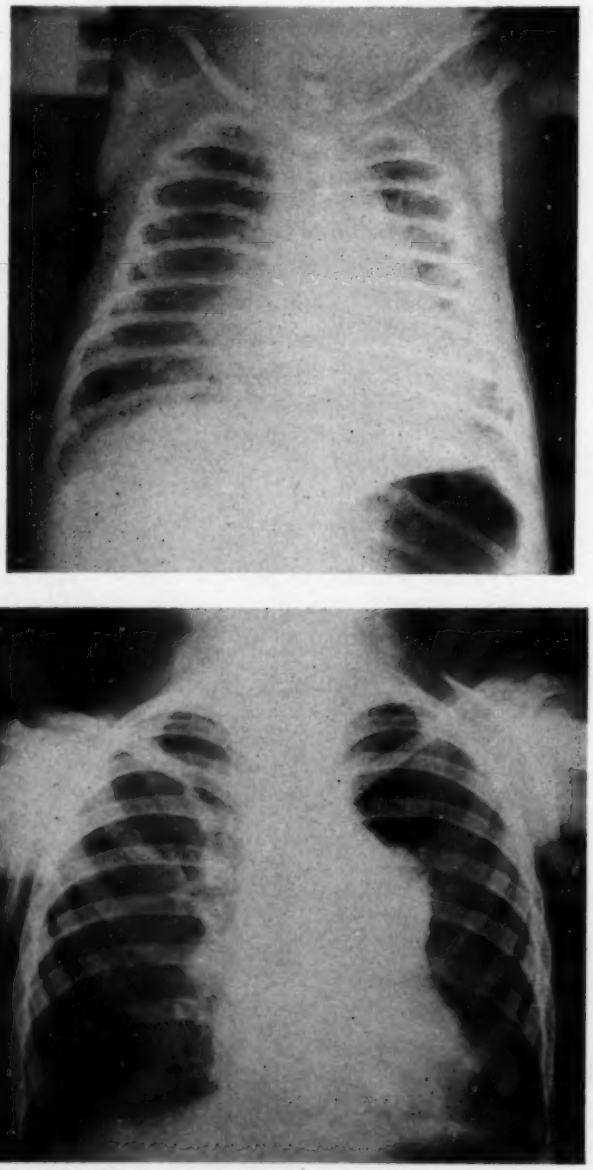


Fig. 8.—X-rays of the chest of L.J. *A*, Taken when 6 days old. Note the heavy vascular markings and very large heart. *B*, Taken when 3½ years old. Note the decrease in heart size, clarity of the lung fields, and huge main pulmonary artery.

Microscopic examination of a lung biopsy was carried out. The lumen:wall ration was 1.13. The small pulmonary arteries appeared definitely hypertrophied, with an increase in muscular and elastic tissue in the media. The adventitia also was increased (Fig. 7). No areas of intimal

proliferation were found. Evidence of heart failure was lacking. The alveoli were clear and capillaries and pulmonary veins were not engorged or dilated.

In both cases cyanosis was noted early. Case 1 appeared cyanotic when in cardiac failure, improved as compensation occurred, and became again cyanotic as he grew older. This patient progressed from a normal newborn state to Phase I and then to Phase II. In Case 2 cyanosis appeared early. At no time was there evidence of failure. He progressed from a normal newborn state directly to an early Phase III. These two cases illustrate clearly the influence of the pulmonary vascular changes on the clinical course of the disease. Variations in the postnatal course are dependent upon whether the pulmonary resistance remains constant or falls. The second case also illustrates the difficulty of differential diagnosis between patients who have a clearcut pulmonary stenosis and those who have peripheral pulmonary vascular obstruction.

CASE 3.—L.J. This 4½-year-old girl appeared normal at birth, but soon after became markedly cyanotic and severely dyspneic. At six days of age an x-ray showed cardiac enlargement (Fig. 8,*A*). During infancy she had "blue spells" characterized by fast, gasping respirations, stupor, and marked cyanosis. These attacks were precipitated by exertion and continued to occur with increasing frequency during her early childhood. Her development was slow. On physical examination she was slightly cyanotic. There was minimal clubbing of the fingers and toes. A marked systolic thrill and loud, harsh, systolic murmur were present maximal in the fourth left intercostal space. The second heart sound at the base was accentuated. On fluoroscopy the heart appeared somewhat enlarged. The pulmonary artery was very prominent, showing vigorous pulsations. Both ventricles were enlarged, particularly the right. The aorta appeared normal in size and activity. X-rays showed a significant decrease in heart size when compared to the film taken in early infancy (Fig. 8,*B*). She died suddenly while playing. At autopsy a wide, short patent ductus arteriosus 3 cm. in circumference was found. The foramen ovale was also patent. There was marked hypertrophy of the right ventricle. The pulmonary artery was greatly dilated and calcium was present in its wall. Microscopic examination of the lungs revealed marked medial hypertrophy of the small and medium-sized pulmonary artery with moderately extensive intimal proliferation. The magnitude of intimal proliferation was significantly greater than that found in the first two cases. In a few areas the small pulmonary vessels appeared quite normal. However, in these same areas there were large pulmonary arteries with excessive intimal change and almost complete obstruction. Within and around the walls of these vessels there was a round-cell reaction suggesting the presence of an arteritis. The lumen:wall ratio was 1.0 (Fig. 9). The pulmonary capillaries and veins were normal in appearance.

The clinical progression from high output failure (Phase I) to a state of compensation and, finally, to a state of complete reversal of the shunt (Phase III) appears to be essentially similar whether a ventricular defect or a defect between the great vessels is present. There is a significant difference, however, in the appearance of cyanosis. In patients with a large ventricular defect or single ventricle, visible cyanosis usually appears early because complete mixing of the arterial and venous blood results in a significant degree of unsaturation, even when the blood flows into the two circulations are equal. In the presence of a patent ductus arteriosus, however, when pulmonary and systemic resistances and blood flows are essentially equal, little or no shunt will occur in either direction, and the arterial blood will be fully saturated. When pulmonary resistance exceeds systemic resistance, differential cyanosis of the upper and lower

parts of the body may become manifest. This finding was not present in Case 3, but in many reported cases of reverse patent ductus, differential cyanosis was a key diagnostic point.

Articles discussing the etiology of the pulmonary vascular changes in patent ductus arteriosus with reversal of blood flow through the ductus are numerous.[18,24,29-48] Many authors have suggested that the combination of

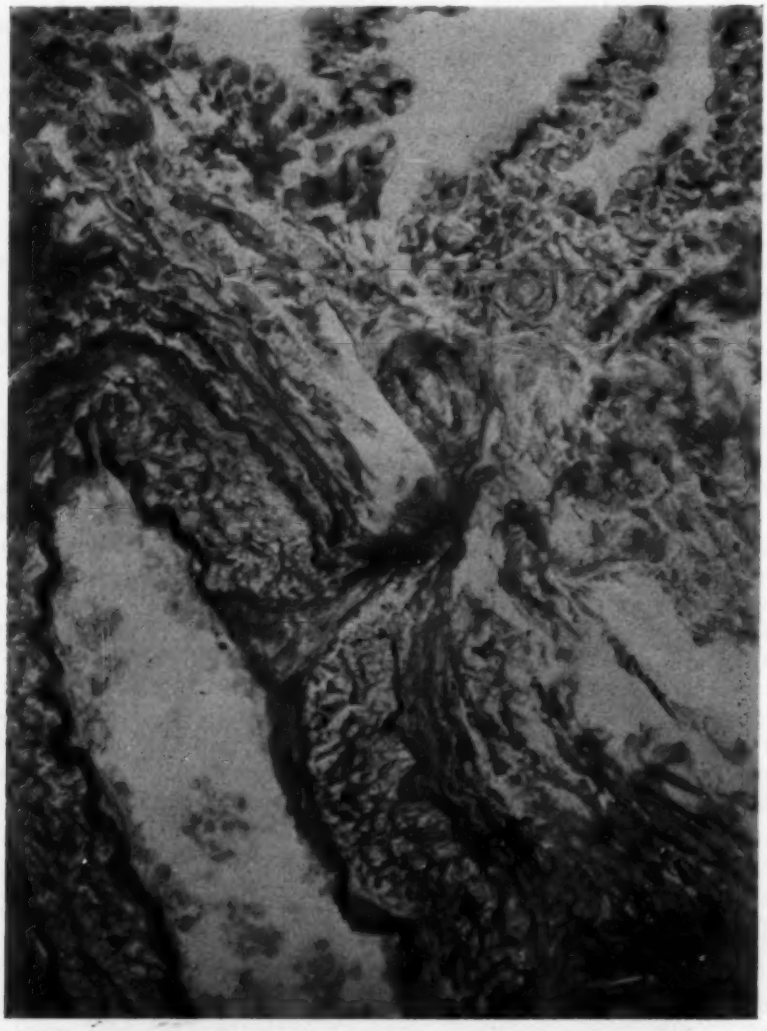
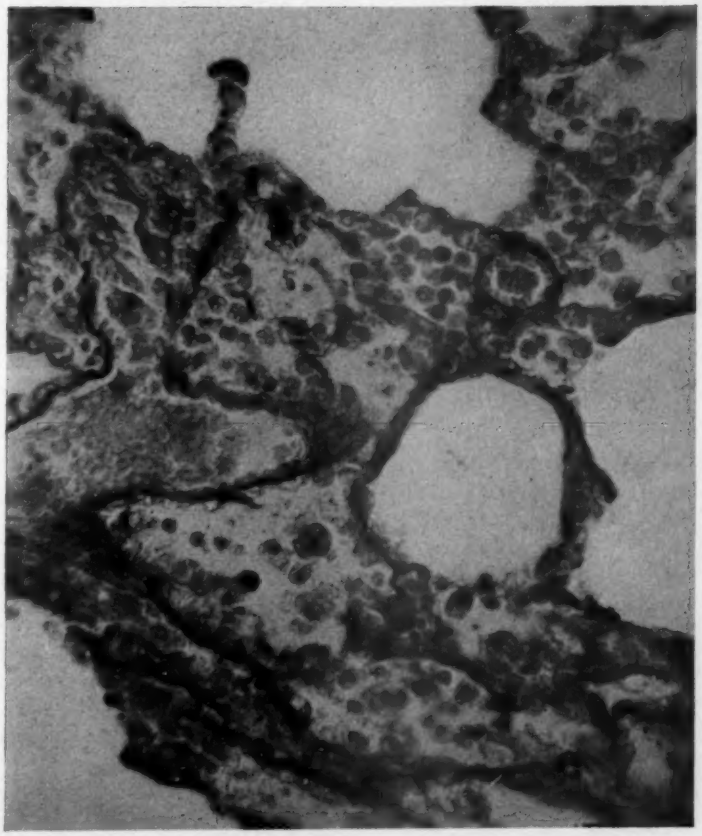


Fig. 9.—Photomicrograph of a small muscular pulmonary artery branching from a larger muscular pulmonary artery obtained from L.J. Note the marked thickness of the media, increase in elastic tissue in the media, and absence of intimal proliferation.

pulmonary vascular disease and patent ductus arteriosus is coincidental. Evidence cited for this hypothesis is the rarity of this combination compared to the incidence of patency of the ductus and the lack of evidence in such cases of a period during early life when a typical continuous murmur and high pulmonary blood flow were present. Also, in many cases cited in the literature the onset

of cyanosis was early. It is not possible to deny the existence of a syndrome of primary pulmonary vascular disease combined with patency of the ductus arteriosus. However, if such a syndrome does exist, it would seem likely that the size of the patent ductus present would be variable and usually rather small. It is striking that in all of the cases we have found reported in the literature, as well as in Case 3 of this report, a very large patent ductus was present. Furthermore, in our patient, the finding of a large heart and vascular lung fields is evidence of left-to-right shunt occurring in infancy. It seems reasonable, therefore, to relate the pulmonary vascular disease which accompanies a large patent ductus arteriosus to the presence of a common ejectile force rather than assuming separate etiological entities.



Figs. 10*A* and *B*.—Photomicrographs of small pulmonary artery obtained from the left and right lung of a 20-month-old infant with "Eisenmenger's complex," a large pulmonary artery to the right lung, and no pulmonary artery to the left lung.

Fig. 10*A*.—Left lung (DL). The artery has a wide lumen and thin wall.

The cause and effect relationship of pulmonary vascular changes and the type of malformation present within the heart is evidenced by the difference between the right and left lung of a patient who died at the age of 20 months. This infant had an agenesis of the left pulmonary artery and a large right pulmonary artery arising from a heart of the "Eisenmenger" type.[51] Because of the cardiac

defect and the absence of a left pulmonary artery, the left lung received a reduced blood supply and the right lung was placed under the stress of a common ejectile force. Lumen:wall ratio determinations from the two lungs are plotted on Graph I. The letters *DL* (Ratio 5.8) and *DR* (Ratio 2.6) represent the ratios obtained from the left and right lungs, respectively. The small pulmonary vessels were thick-walled and small-lumened in the right lung, but appeared thin-walled and large-lumened in the left lung (Figs. 10*A* and *B*). In

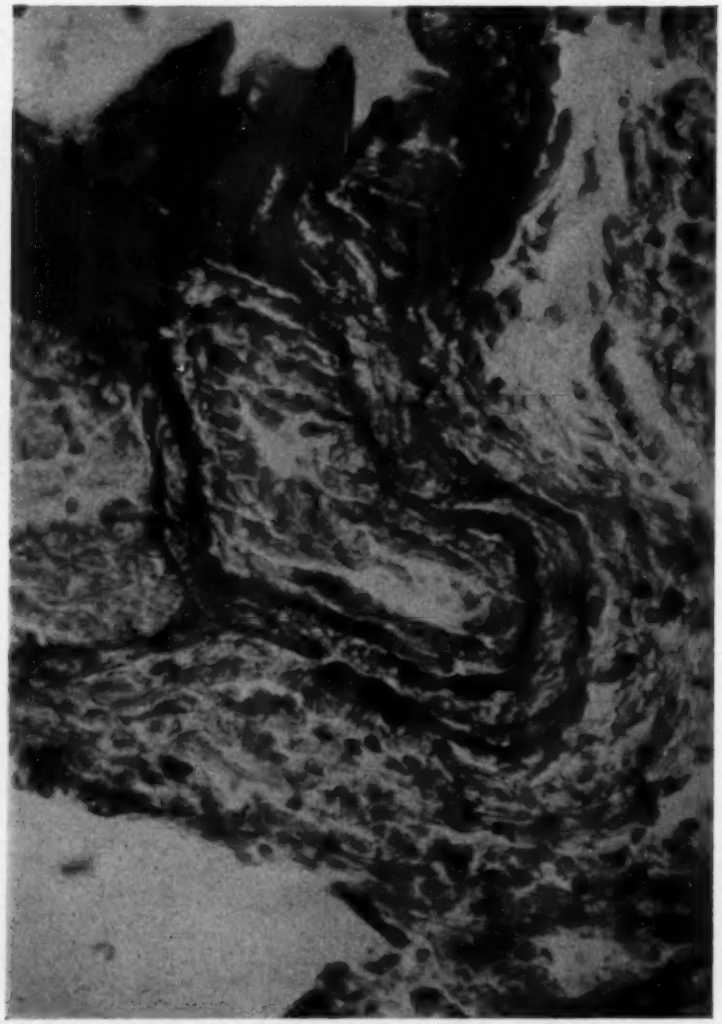
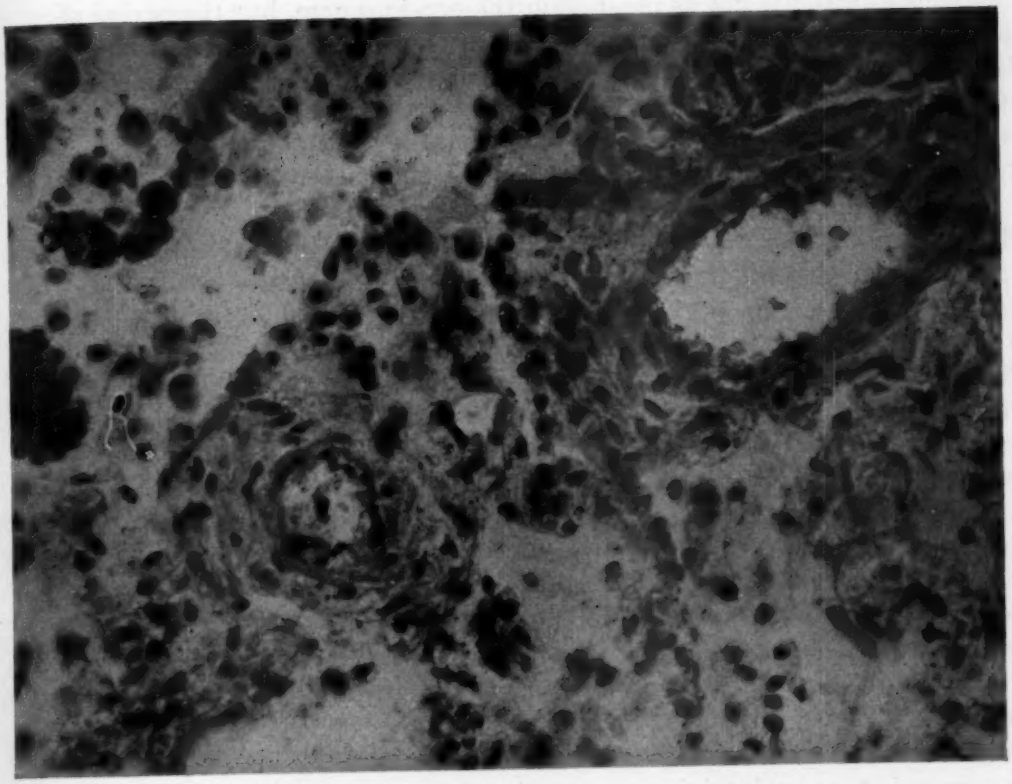


Fig. 10*B*.—Right lung (DR). There is marked medial hypertrophy.

the same graph the letters *PL* (Ratio 3.0) and *PR* (Ratio 4.3) represent the ratios obtained from the left and right lungs, respectively, of a 4-year-old child who died in cardiac failure nine months after a left Potts anastomosis had been done for a tricuspid atresia. At autopsy it was noted that the origin of the left pulmonary artery from the main pulmonary artery was constricted so that the anastomosis directed blood from the aorta almost entirely into the left lung.



B.

A.

Fig. 11.—Photomicrographs of small pulmonary arteries obtained from the right and left lungs, respectively, of a 4-year-old child with a tricuspid atresia following the creation of a Potts-Smith anastomosis directing blood to the left lung only. *A*, Right lung (PR). The artery is thin-walled with a large lumen. *B*, Left lung (PL). There is a definite medial hypertrophy. Evidence of cardiac failure is present in both sections.

The difference in ratios is not as great as in the previous case, but the period of time during which the left lung was subjected to the stress of high pressure and high flow was only nine months. Photomicrographs of a small artery from each lung of this patient are shown in Figs. 11*A* and *B*.

SURGICAL CONSIDERATIONS

The similarity in the life cycle of patients with a large ventricular septal defect, single ventricle, large patent ductus, or aortic septal defect is not surprising. All have a common ejectile force. All with varying speed pass from birth to Phase I or directly to Phase II. And, those who survive Phase I pass into Phase II or Phase III. This progression of clinical signs and symptoms is of more than academic interest, for we are in a position to interrupt this life cycle, if we so desire, by means of surgical intervention. Early surgery is frequently life-saving for patients in Phase I. A patent ductus can be closed in early infancy, and it may soon be possible to close a ventricular septal defect. If correction of the defect is not possible, pulmonary blood flow may be reduced and the work of the heart relieved by the artificial creation of pulmonary stenosis.[14,26,27,49] A high resistance placed in the main pulmonary artery can compensate for the low resistance in the peripheral vascular bed and so bring pulmonary and systemic blood flows into better balance. Such a surgical approach is palliative, not corrective. However, by the creation of pulmonary stenosis, cardiac failure can be effectively treated and the progression of pulmonary vascular changes can be arrested, thus maintaining a normal pulmonary vascular bed, pending the time when the correction of the defect becomes practical.

Patients in Phase II should also be operated upon, for in this phase the narrowing of the pulmonary vessels is primarily due to medial hypertrophy and not to intimal sclerosis. Our own postoperative catheterization results[14,26,49] and data reported by others[50] suggest that once the effect of a common ejectile force is removed, the hypertrophy of the media of a small pulmonary artery may recede. When the shunt is predominately left to right, and when the diastolic pressure is lower in the pulmonary artery than in the aorta, correction of the defect or the creation of pulmonary stenosis, a palliative procedure, is indicated. It is perhaps too late to operate when Phase III has been reached, for in such patients excessive intimal proliferation is common, and it is difficult to visualize a significant decrease in this intimal proliferation. We do not know when, in the course of the disease, pulmonary vascular changes become so severe that operation is no longer indicated and may even be contraindicated.

SUMMARY AND CONCLUSIONS

In malformations of the heart in which there is a large communication between the ventricles or great vessels, systolic pressures in the pulmonary and systemic circulation are equal and a common ejectile force is present. In such patients the clinical course and prognosis is governed by the state of the pulmonary vascular bed.

A study of anatomic alterations found in the small pulmonary vessels confirmed the theoretical concept that there are three courses which the pulmonary vascular bed may follow after birth, resulting in three different clinical syndromes or phases.

Phase I.—Following birth the thin-walled, small-lumened, fetal pulmonary arteries thin out. Pulmonary resistance falls. Pulmonary blood flow, therefore, increases, eventually leading to high-output cardiac failure.

Phase II.—Following birth the fetal pulmonary arteries retain or regain their fetal state. A high pulmonary resistance is thus retained. The pulmonary and systemic circulations remain in balance. Signs and symptoms are minimal or absent.

Phase III.—Fetal pulmonary arteries become narrower due to progressive medial hypertrophy and intimal sclerosis. Pulmonary resistance exceeds systemic resistance. A right-to-left shunt is present.

Thus, in malformations of the heart associated with a common ejectile force, there exists a characteristic life cycle which is dependent upon an excessive, a controlled, or a reduced pulmonary blood flow.

An understanding of the important role of the pulmonary vascular bed in governing the clinical course of the disease is essential to the rational application of corrective surgical procedures. Corrective or palliative surgery may be lifesaving for patients in Phase I. In Phase II surgery may prevent the progression of pulmonary vascular changes. During Phase III the extreme nature of the pulmonary vascular changes may nullify any possible gain to the patient from a cardiac operation.

SUMMARIO IN INTERLINGUA

Un analyse del proportion passage: pariete e de datos clinic in patientes in qui il existe un major communication inter le ventriculos o le grande vasos indica que le curso clinic e le prognose in tal casos es governate per le stato del vasculatura pulmonar. Le arterias pulmonar pote allargar se e disveloppar parietes tenue, illos pote remaner fetal in lor structura o pote disveloppar un progressive spissification medial e intimal. In consequentia le resistentia pulmono-vascular pote diminuer se, remaner constante, o accrescer. Proque, in le presentia de un major communication inter le duo ventriculos o grande vasos, il existe un commun fortia de ejection, le fluxo sanguinee verso le pulmones depende del resistentia pulmonar. Per consequente, le aspecto clinic depende de si le fluxo pulmonar es excessive, regular, o reducite. Le recognition de iste rolo importante del vasculatura pulmonar es essential pro le application rational de corrective mesuras chirurgic.

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THE VECTORCARDIOGRAM IN INFERIOR MYOCARDIAL INFARCTION. IV

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INTRODUCTION

THIS study is concerned with a description of the vectorcardiogram in "inferior" myocardial infarction. It was undertaken to supplement the morphologic description of planar vectorcardiograms[1,5] and to obtain measurements of the QRSsÊ loop. In addition, the S-T junction (J) was studied and measurements of the TsÊ loop were made. The relationship of the QRS to the T vectors is presented. The PsÊ loop is not described.

The electrocardiographic findings will be discussed.

METHODS AND MATERIALS

Thirty subjects form the basis of this report. A complete electrocardiogram was taken at the time when the vectorcardiogram was obtained. The latter comprised a horizontal, sagittal, and frontal planar projection using the trihedron reference system of Duchosal, but with positive polarity.[3] No adjustment in circuit sensitivity was made for unequal vertical dimensions of the reference frame.

The instruments and techniques used have been described previously.[4]

The terms right, left, anterior, posterior, superior, and inferior refer to the patient in the sense used by Grishman and others.[5]

The QRSsÊ loop was arbitrarily divided into initial forces, body, and terminal appendage. The initial forces are defined as those at the beginning of the QRSsÊ loop which are oriented to the right and/or superior to zero. The terminal appendage is arbitrarily taken to mean the forces at the end of the QRSsÊ loop which are oriented to the right and/or superiorly. The initial forces and terminal appendage correspond in a general way to Q or S waves, respectively, and are of great diagnostic value.

The body of the QRSsÊ loop was composed of a centrifugal and centripetal limb joining the initial forces and the appendage. The body had a leftward and inferior position, and was usually oriented both anteriorly and pos-

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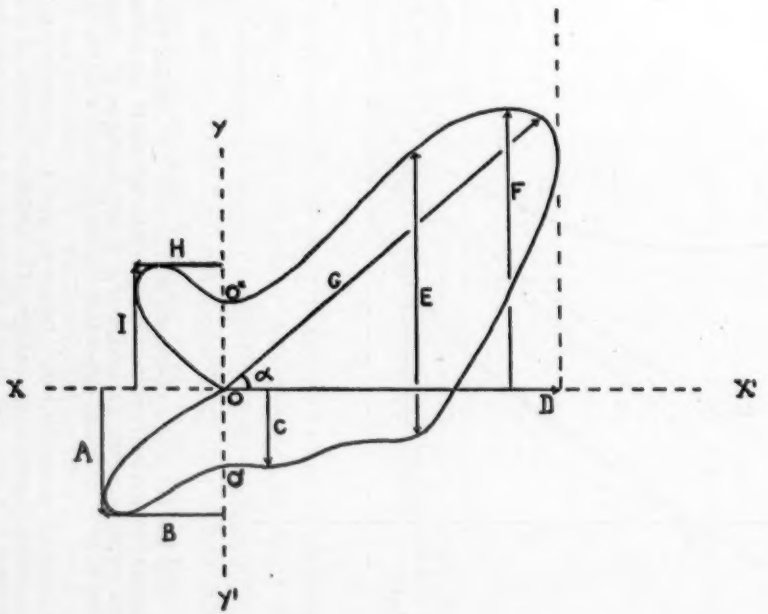

Fig. 1.

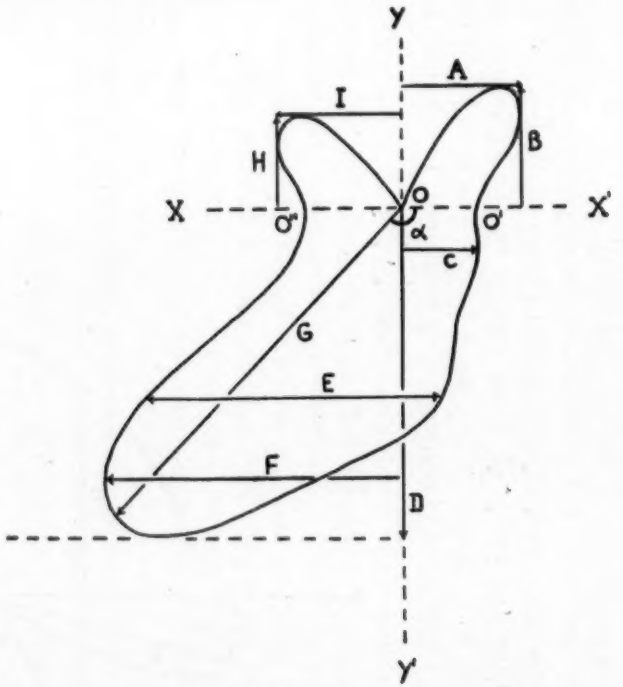

Fig. 2.

Fig. 1.—Horizontal projection. *O* at the point of intersection of *XX'* and *YY'* equals the point of origin of the cardiac vector. *G* equals maximal vector. Long axis equals angle subtended by maximal vector (*G*) and *XX'*. Initial forces is that part of the trace starting at *O* and ending at *O'*. Body equals the trace starting at *O'* and ending at *O''*. Terminal appendage equals the trace starting at *O''* and ending at *O*.

Perpendicular projections of maximal dimensions of: Initial forces: *A* = anterior, *B* = right; Body: *C* = anterior, *D* = left, *E* = width, *F* = posterior; Terminal appendage: *H* = rightward, *I* = posterior.

Fig. 2.—Sagittal projection. *O* at the point of intersection of *XX'* and *YY'* equals the point of origin of the cardiac vector. *G* equals the maximal vector. Long axis equals angle subtended by maximal vector (*G*) and *XX'*. Initial forces equal the trace starting at *O* and ending at *O'*. Body equals the trace starting at *O'* and ending at *O''*. Terminal appendage equals the trace starting at *O''* and ending at *O*.

Perpendicular projections of maximal dimensions of: Initial forces: *A* = anterior, *B* = superior; Body: *C* = anterior, *D* = inferior, *E* = width, *F* = posterior; Terminal appendage: *H* = superior, *I* = posterior.

teriorly. It was equally divided into three portions in the horizontal and sagittal planes: proximal (contiguous to zero), middle, and distal.

The right-left, anterior-posterior, and superior-inferior displacements of the maximal vectors in the horizontal, sagittal, and frontal planes were obtained by dropping perpendiculars from the heads of these vectors to the horizontal or vertical lines drawn through zero, as shown in Figs. 1 to 3. The actual lengths of the maximal vectors in the frontal plane were also measured, in addition to

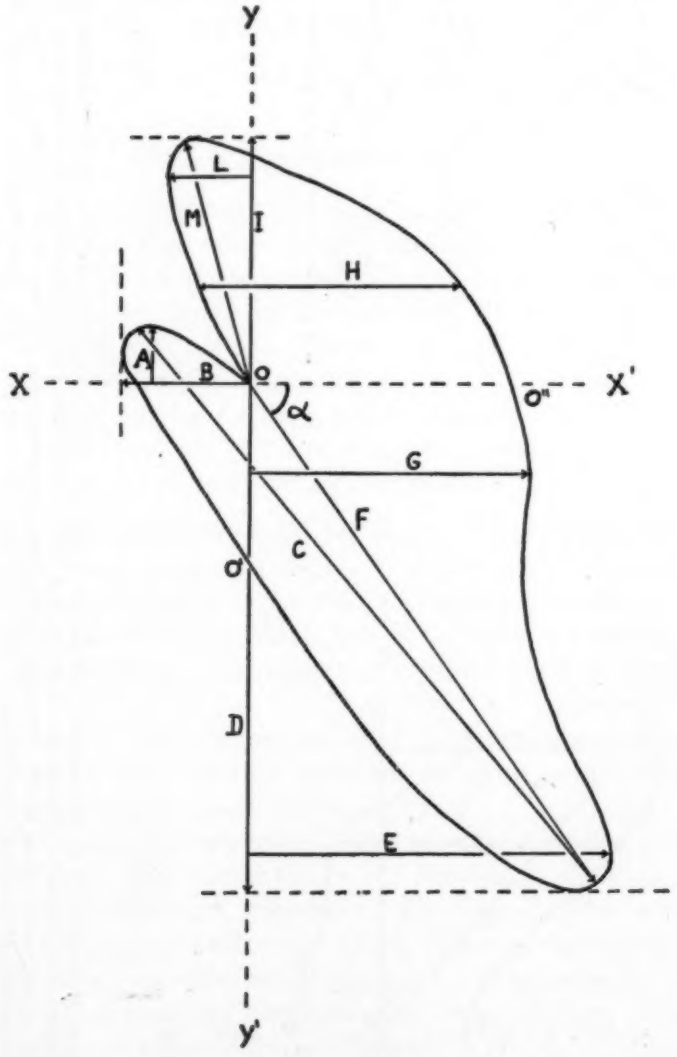

Fig. 3.—Frontal projection. *O* **at the point of intersection of** *XX'* **and** *YY'*, **equals the point of origin of the cardiac vector.** *F* **equals the maximal vector. Long axis equals angle (α) subtended by maximal vector** *F* **and** *XX'*. **Initial forces equal the trace starting at** *O* **and ending at** *O'*. **Body equals the trace starting at** *O'* **and ending at** *O''*. **Terminal appendage equals the trace starting at** *O''* **and ending at** *O*.

Perpendicular projections of maximal dimensions of: Initial forces: *A* **= superior,** *B* **= right; Body:** *D* **= inferior,** *E* **= left,** *G* **= width; Terminal appendage:** *H* **= width,** *L* **= right,** *I* **= superior; Largest vector:** *C* **= sum of initial forces and body (not done in this series),** *F* **= body (maximal vector in normal subject),** *M* **= appendage (not done in this series).**

the right-to-left and superior-to-inferior displacement, as shown in Fig. 3. Other measurements were made as indicated in Figs. 1 to 3 and their corresponding legends. This same method of analysis was applied to the study of the normal vectorcardiogram.[4]

Patients whose vectorcardiograms displayed greater than normal[4] initial superior forces were chosen for this study. Vectorcardiograms in which the initial rightward, anterior, and posterior forces were abnormal, and those in which the initial superior forces were oriented entirely to the left, were excluded. These features were usually associated with multiple areas of infarction, as shown by autopsy,[6] or suggested by electrocardiography.[7] This method of selection was used in an attempt to exclude all but isolated inferior wall myocardial infarction; septal involvement was probably present in some cases.

The criteria[4] for the normal magnitude and duration of initial superior forces varies with angle α (position of the maximal vector in the frontal plane), and these factors were taken into consideration in the selection of cases (Tables I and II). Since normal vectorcardiograms occur in which the initial forces are inferiorly oriented before assuming a superior direction, vectorcardiograms were included in which the initial forces were similarly disposed, providing the subsequent superiorly directed forces were abnormal as defined above (Tables I and II).*

TABLE I. THE MAGNITUDE AND DURATION OF NORMAL FRONTAL INITIAL SUPERIOR QRS FORCES ACCORDING TO ANGLE α (MAXIMAL VECTOR)

ANGLE	DURATION (SEC.)	MAGNITUDE (MILLIVOLT)
>+55°	0.0275	
+55°	0.015	
+45°	0.0075	
+35°	0.005	
<+35°	0	
+65° or more		0.394
<65°		0.105

Note that the value increases as angle α is more vertical.
In addition to these, there were some instances, in the normal vectorcardiogram, in which the very beginning of the QRS went inferior before reversing its direction to a more superior orientation, though usually without going above zero. These latter forces were either counterclockwisely inscribed or figure of eight in configuration.

All patients had a past or present clinical picture consistent with coronary heart disease. Hypertension was present in some of them, but the presence of other etiological types of heart disease excluded the patients from this study.

In all patients the electrocardiograms taken prior to or at the time the vectorcardiogram was obtained presented one or more serial changes considered diagnostic of inferior myocardial infarction: the appearance of a Q wave in Lead aV_F in place of an initial R; symmetrically, deeply inverted T waves; and characteristic S-T segment displacement in Leads II, III, and/or aV_F.

*All measurements of millivolts referred to in the text and tables should be divided by 2 to obtain the actual values recorded on the oscilloscope.

TABLE II. THE MAGNITUDE AND DURATION OF FRONTAL PLANE SUPERIOR INITIAL FORCES IN TWENTY-FOUR OF THE THIRTY CASES OF INFERIOR MYOCARDIAL INFARCTION

ANGLE	DURATION (SEC.)	MAGNITUDE (MILLIVOLT)
+33°	0.0275	0.256
− 9°	0.03	0.315
+10°	0.015	0.055
+44°	0.035	0.380
+35°	0.030	0.370
+50°	0.020	0.185
+72°	0.0325	0.420
+26°	0.0325	0.315
+60°	0.0350	0.315
+18°	0.0325	0.425
+74°	0.025	0.475
−10°	0.020	0.09
+25°	0.030	0.245
− 5°	0.030	0.055
+22°	0.02	0.09
−15°	0.0525	0.094
+38°	0.03	0.137
+45°	0.025	0.368
+42°	0.0225	0.316
+45°	0.02	0.132
+30°	0.025	0.180
+35°	0.03	0.20
+ 8°	0.025	0.150
+10°	0.025	0.140

In addition to these, there were six cases in which initial forces were inferiorly oriented before going superiorly. These latter superior forces were abnormal as indicated in Table I and text.

However, the diagnosis of inferior myocardial infarction was not always possible on the basis of the single electrocardiogram taken at the time the vectorcardiogram was obtained (see below).

At least one of the following additional confirmatory signs of myocardial infarction was noted in each case: fever, leukocytosis, increased sedimentation rate, and post-mortem findings.

RESULTS

1. *QRS Loop.*—

Horizontal Plane.—Fifteen loops were smooth, slightly flattened ovals with a moderate amount of posterior bulging and were indistinguishable from the normal in all respects. The traces in six cases were circular, resembling left ventricular hypertrophy. In several the loops displayed an irregular contour, i.e., indentations (excavations) and outpocketings. The former deformity was usually slight, and was noted in the first third of the body in five cases (Fig. 4); single or multiple outpocketings were mostly confined to the appendage (Fig. 5).

The maximal duration of QRS was 0.115 second. The early and/or late vectors in one-fourth of the cases were inscribed with abnormal slowness, the former as much as 35 per cent, the latter as much as 65 per cent of the total duration of QRS. In one vectorcardiogram terminal slowness of inscription

began in the distal part of the efferent limb of the body, in another in the most distal portion of the afferent limb near the tip.

All portions of the loop were generally counterclockwisely inscribed, except in seven with superimposition of the initial forces (Fig. 4), one with a figure-of-eight configuration of the distal body, and one with a figure-of-eight appendage.

The long axis* varied from −25 to +18 degrees in contrast to the normal of −8 to +18 degrees. Thus, some loops differed from the normal in being more posteriorly displaced.

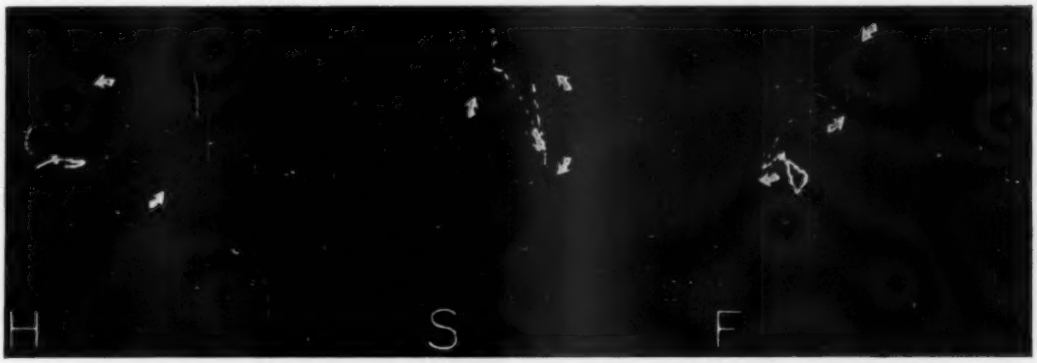

Fig. 4.—The horizontal and frontal planes are photographed so as to show detail of the initial forces which are superimposed in the horizontal plane and are oriented inferiorly before going clockwisely superiorly in the frontal plane. Note the large sweep of initial frontal superior forces. The initial and early frontal plane forces describe a deep, inferiorly directed concavity.

Fig. 5.—The terminal rightward appendage in the horizontal plane displays a slowly inscribed irregular contour. The initial frontal forces, not visualized in this photograph, are inferiorly oriented before going superiorly in a clockwise direction (similar to Fig. 4). Initial forces in the sagittal plane are counterclockwisely inscribed.

Initial forces: There were initial rightward and entirely anterior forces in all cases. They formed a hemioval with minimal anterior displacement of the efferent limb, and greater anterior orientation of the afferent limb. In seven vectorcardiograms with large, though not abnormal rightward forces, both

*The long axis is the angle subtended by the horizontal line drawn through the zero point and the maximal vector, and is 0 degrees when the maximal vector coincides with the horizontal line, positive when it is anteriorly, and negative when posteriorly displaced.

limbs were superimposed due to slight anterior displacement of the afferent limb (Fig. 4). Superimposition of these limbs is abnormal except when the initial forces are minimal.[4] The efferent limb in two cases went sharply anteriorly, but did not exceed the normal in magnitude (Fig. 6).

The magnitude and duration of the initial rightward and anterior forces were within the normal range in all cases.

Body: The body of the loop varied from a hemioval to circular configuration. Superimposition of afferent and efferent limbs did not occur, although figure-of-eight configuration was present in the distal third in one case. The portion beyond the crossover was very narrow. Varying portions of the proxi-

Fig. 6.—Initial forces in the horizontal plane go acutely anterior rather than straight to the right. The maximal horizontal vector is more posterior than normal. The initial frontal forces dip slightly inferiorly before going superiorly in a clockwise direction. There is a large sweep of right-to-left vectors of initial superior frontal forces.

Fig. 7.—There is slow inscription associated with irregularities along the efferent limb of the body in the horizontal plane. The sagittal plane is partially counterclockwisely inscribed. The initial frontal forces are inferior before going superior in a clockwise direction. The main portion of the frontal loop is superior except for an inferior dip that occurs abruptly and is associated with rapid changes in orientation of vectors. The large vectors below the zero point in the sagittal and frontal plane are P loops.

mal part of the efferent limb of the body were anterior to the zero point in all tracings; nevertheless, posterior displacement occurred early, though never abruptly, in some cases.

Figs. 7 and 8 show irregularities of the body beyond the proximal portion (first third). Slowness of inscription occurred in areas of irregularity close to the end of the efferent limb in two cases (Fig. 7), and near the beginning of the

afferent limb in one (Fig. 8). These vectorcardiograms represent the most bizarre patterns in the horizontal plane.

Measurements of the body fell within the normal range except for the posterior displacement, width, and/or duration in some.

Terminal appendage: A terminal appendage occurred in thirteen cases and was always entirely posterior; it varied from a hemioval to a linear projection. In one instance the distal portion of the appendage was very narrow and displayed a crossover. Irregularities of contour in association with slowness of inscription were common, contrasting to the invariably smooth contour of the normal (Fig. 5). The magnitude of the rightward deviation and duration of the appendage did not exceed the normal[4]; the posterior displacement was excessive in four.

Fig. 8.—There is irregularity associated with slow inscription in the afferent limb of the body in the horizontal plane. Initial frontal forces are entirely superiorly and clockwisely inscribed. Although the frontal initial and early vectors are clockwisely inscribed, there is a sudden change to counterclockwise inscription in association with a broad terminal superior appendage. This patient has left ventricular hypertrophy.

Sagittal Plane.—The contour in more than half the vectorcardiograms resembled the normal in that the loops were smooth, slightly flattened ovals with a variable amount of terminal bulging posteriorly. Less than half of the sagittal traces displayed one or more irregularities consisting of outpocketings and complex crossovers. The latter were especially prone to occur during the mid- and late portion of the trace and were often associated with slowness of inscription (Figs. 7 and 9). The maximal duration of QRS was 0.115 second. The early and late vectors, with few exceptions, were more slowly inscribed than the rest of the loop, the former up to 35 per cent, the latter as much as 80 per cent of the total duration of QRS. However, some loops showed no abnormal slowness whatsoever. There were nine vectorcardiograms with normal clockwise inscription (Fig. 6) throughout, and four with entirely counterclockwise inscription (Fig. 10). There were two with counterclockwise inscription of initial superior forces and clockwise inscription of the body (Fig. 11); the reverse was not noted. The remaining traces showed several changes in direction of inscription of the body, often in association with crossovers and slow inscription, and presented a complex pattern (Fig. 7 or 12).

The long axis* varied from +95 to −150 degrees compared to +97 and +102 degrees in the normal,[4] and thus in some instances was more negatively oriented.

Initial forces: The superior initial forces were often entirely anterior and formed a clockwisely inscribed hemioval, resembling the normal in these two respects. Exceptions occurred in four in which a figure-of-eight configuration was noted. A figure-of-eight configuration is significant whenever the magnitude of the initial forces is greater than just minimal,[4] as in the four cases mentioned. There were four vectorcardiograms in which, in marked contrast to

Fig. 9.—The late portions of sagittal vectors cross upon themselves, are slowly inscribed, and reach a posterior orientation rather abruptly. The corresponding vectors are "rounded" posteriorly in the horizontal plane, while there is an upward convexity of late forces in the frontal plane. Initial superior frontal forces display great magnitude and duration. They describe a broad sweep.

Fig. 10.—The terminal rightward appendage in the horizontal plane displays irregularity of contour and is slowly inscribed. The sagittal plane is circular and counterclockwisely inscribed. Initial frontal forces are superior and clockwise in direction.

the normal, the initial superior forces were counterclockwisely inscribed (Fig. 11). In these the efferent limb was anterior, the afferent portion posterior. Although the efferent limb tended to go straight up (Fig. 9), some deviated anteriorly to a moderate degree.

There were six instances in which the earliest vectors were inferiorly oriented before assuming a more superior orientation and rising above the zero point

*The long axis, the angle subtended by a horizontal line drawn through the zero point and maximal vector, is + 90 degrees when the maximal vector is perpendicular and inferior to the horizontal line, less than +90 degrees when anteriorly displaced, and greater than +90 degrees when posteriorly displaced.

(Fig. 7). Among the six vectorcardiograms, the greatest inferior vector was 0.11 millivolt and occurred 0.01 second after the onset of QRS, as in the normal. However, in contrast to the normal, the following vectors rose above zero. In all but one of them the superior vectors exceeded the preceding inferior forces in magnitude. In three of the six cases the initial inferior-superior forces were counterclockwisely inscribed (Fig. 7).

Measurements of the initial superior forces differed in all cases from the normal, in that the superior forces were greater in magnitude and/or duration in relation to angle α in the frontal plane. A further discussion of these relationships will be detailed in the frontal plane.

Fig. 11.—Initial horizontal forces are superimposed. Initial superior sagittal forces are counterclockwisely inscribed, but the remainder of the loop is clockwise. The entire frontal plane is clockwise except for a tiny superior terminal appendage. The frontal plane is unusual in that it displays no crossovers with this pattern (see text).

Body: There was great variation in the form of the body (Figs. 4 to 6). Eight were circular, resembling left ventricular hypertrophy (Fig. 10). Crossovers occurred in all portions, and unlike the normal, the part distal to the crossover was circular in four (Fig. 7). In most cases the efferent limb of the body was in part anterior to zero, but in ten cases the body was entirely posterior and the initial forces in these were counterclockwisely inscribed and partly posterior (Figs. 7 and 11).

There were three instances in which the initial clockwisely inscribed forces and the proximal portion of the efferent limb of the body were anterior, but the latter part of the body deviated abruptly to a posterior orientation and displayed slow inscription associated with a crossover (Fig. 9).

Measurements of the body in the sagittal plane were normal, or displayed greater posterior displacement and/or duration.

Terminal appendage: Sixteen patients had a terminal superior appendage which varied from a hemioval to figure-of-eight configuration and was always entirely posterior. There were five cases in which the loop was entirely or almost entirely superior and counterclockwisely inscribed; in one the beginning of the initial forces, in another the end of terminal vectors, and in a third both initial and terminal forces went slightly inferiorly (Figs. 5, 7, and 10).

In four instances one or more measurements of the superior terminal appendage exceeded the normal: superior deviation, posterior deviation, and total duration of the appendage.

Frontal Plane.—The loops in this projection displayed the greatest variability. The configuration varied from a circular form to a flattened ellipse, or displayed one or more crossovers. In contrast to the normal, outpocketings and indentations usually occurring in the mid- and late portions of the loop, were not uncommon and were often associated with changes in direction of inscription of the trace. The early and late forces were usually slowly inscribed, the former up to 35 per cent, the latter as much as 80 per cent of the total QRS.

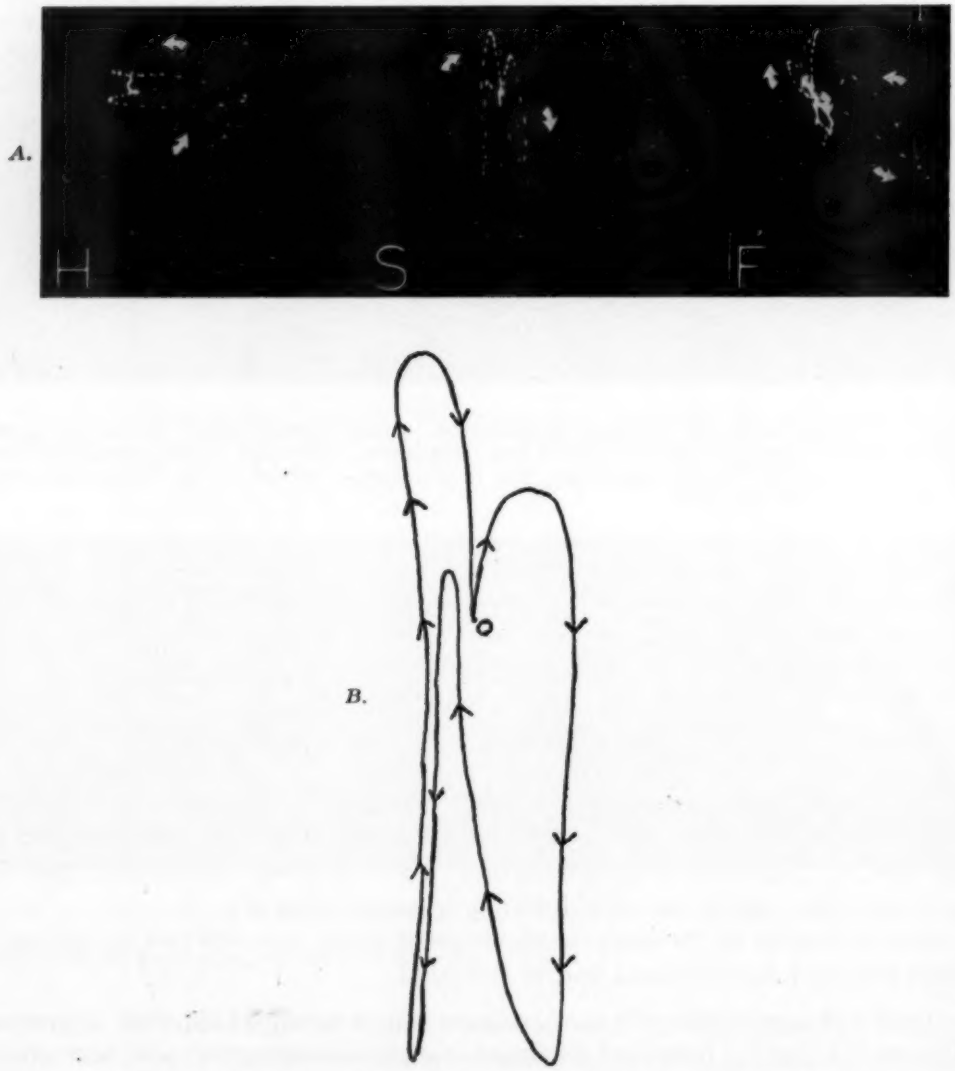

Fig. 12.—The terminal rightward, slowly inscribed horizontal vectors display a crossover and reach the zero point from a 90 degree position. The mid-vectors go above zero in the sagittal and frontal plane. They then dip inferiorly where they are superimposed before going superior terminally. To understand the inscription of the sagittal plane, see *B* for sequence of inscription of sagittal plane of *A*.

Unlike the normal, it was not uncommon to find slowness of inscription in various parts of the QRS, often associated with rapid changes in direction (Fig. 7). However, at times unusual slow inscription was not noted in any part of the loop.

The initial forces were always clockwisely inscribed, and the rest of the loop either clockwisely or counterclockwisely inscribed.

Initial forces: The initial forces went to the right in all cases and the rightward component was invariably normal in both magnitude and duration. The first vectors in twenty-four of the thirty subjects were superiorly oriented; their magnitude in all, and their duration in all but two, exceeded the normal (Tables I and II).

In six cases the earliest vectors went to the right and inferiorly before reversing their direction to a rightward superior orientation. These vectors were always inscribed clockwisely, as in the other twenty-four cases (Fig. 4). The greatest inferior deviation among the six vectorcardiograms was 0.11 millivolt, and occurred 0.01 second after the onset of QRS, i.e., within normal limits. However, the subsequent forces were abnormal inasmuch as they rose above zero. Moreover, with the exception of one case, the maximal superior initial vectors always exceeded the inferiorly oriented initial vectors. The six traces were the most horizontal loops of the series, the greatest (angle α) being +24 degrees. Normal loops with angle α +35 degrees or less do not display any superiorly oriented initial forces.[4]

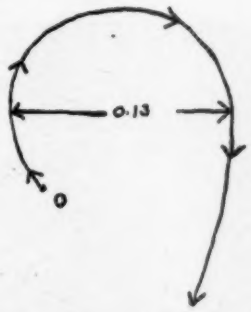

Fig. 13.—The greatest sweep of normal frontal initial forces is 0.13 millivolt.

The afferent and efferent limbs of the initial forces were more widely separated than the normal, in which close approximation, figure-of-eight configuration, or superimposition are common. The latter forms were not observed in any of the cases of the present series.

In the normal the greatest left-to-right distance between the afferent and efferent limbs of superior clockwisely inscribed initial forces, measured along a line parallel to the horizontal axis, was 0.13 millivolt (Fig. 13). This measurement exceeded the normal in nineteen of the cases of inferior myocardial infarction; in four cases the morphology of the loop was such that this measurement could not be made.

Body: The body of the frontal plane QRS loop, as noted above, varied greatly in form. Although some loops retained the smooth configuration of the normal vectorcardiogram, others displayed irregularities, such as outpocketings, indentations, and rapid changes in direction, at times associated with slow inscription (Figs. 7, 9, and 12). Portions of the loop distal to a crossover were often circular, differing in this respect from the normal (Fig. 7).

The direction of inscription of the body followed the normal relationships, i.e., the more horizontal loops were counterclockwisely and the more vertical tracings clockwisely inscribed. The smallest angle α associated with clockwise inscription was +18 degrees, the greatest angle α associated with counterclockwise inscription was +25 degrees. In three instances the early part of the body as well as the initial forces were inscribed clockwisely; in these the direction of inscription changed to counterclockwise, although crossovers did not occur (Fig. 4). This unusual pattern was never found in the normal or in left ventricular hypertrophy. Measurements of the body differed from the normal in that the duration and/or width of the body exceeded the upper limits in six cases.

Terminal appendage: A terminal superior and/or rightward appendage occurred in twenty-two vectorcardiograms: these were oriented to the right and superiorly in seven, to the right and inferiorly in six, and to the left and superiorly in nine. In four vectorcardiograms the superior terminal appendage dipped slightly inferiorly before returning to zero. As noted in the sagittal plane, there were five cases in which the loop was superior, or almost entirely so (Fig. 4).

Fig. 14.—The QRS in the horizontal and sagittal planes resembles the normal. The terminal rightward forces in the frontal plane make a figure-of-eight configuration.

Appendages were variously inscribed, but there were three instances of an unusual pattern in which the entire loop showed no crossing and was clockwisely inscribed except for a terminal superior appendage that was counterclockwisely traced (Fig. 4). This lack of crossover as contrasted with the normal is partly due to the large left-to-right sweep of superior initial forces (Fig. 4).

Some terminal appendages revealed unusual patterns, such as figure-of-eight configuration of rightward and inferior forces (Fig. 14), or peculiar pinch-offs, associated with slow inscription (Fig. 15).

Measurements of the terminal appendage exceeded, in some instances, the normal upper limits of superior magnitude and/or duration of these forces.

2. *T Loop and S-T Junction.*—

The actual length of the maximal T vector fell within the normal range except in six subjects in whom the maximal T vector in the sagittal and/or frontal

plane exceeded the normal upper limit. In five cases the T loops differed from the normal in being round, i.e., their widths approximated their lengths. Six vectorcardiograms displayed arc-shaped T loops similar to those found in left ventricular hypertrophy.

The T loops were inscribed clockwisely in three and counterclockwisely in eleven in the horizontal plane, clockwise in ten and counterclockwise in four in the sagittal plane, and clockwise in five and counterclockwise in seven in the frontal plane. The direction of the T loop was not ascertainable in every vectorcardiogram.

The maximal vector of the T loop varied from +172 to −177 degrees in the horizontal plane, +120 to −90 degrees in the sagittal plane, and −170 to +160 degrees in the frontal plane. These measurements exceeded the normal in both positive and negative positions in all planes.

The angle between the maximal QRS and T vector displayed great range in contrast to the normal.

Fig. 15.—The superior initial forces in the frontal plane display a large right-to-left sweep. The terminal frontal forces show a peculiar pinch-off rather than displaying the smooth normal contour.

The S-T segment junction showed no characteristic position being right, anterior, up in five; right, posterior, up in thirteen; right, posterior, down in two; right, anterior, down in two; left, posterior, down in two; and not displaced in three. In twenty-four the S-T junction displacement exceeded the normal.

3. *Electrocardiographic Findings.—*

The electrocardiograms were evaluated according to the criteria of Myers and associates,[8] and Goldberger.[9] Nineteen electrocardiograms failed to fulfill the criteria for the diagnosis of inferior (posterior) myocardial infarction stated by both these authors. Included among these nineteen were six electrocardiograms in which the initial QRS deflection in aV_F was a small R wave. This incidence is identical to that found by Myers and associates,[8] namely, 20 per cent in a series of 110 autopsied patients. The electrocardiograms in eleven of our cases displayed the diagnostic signs of inferior myocardial infarction; four

fulfilled the criteria of both authors, three those of Myers, and four those of Goldberger.

In six patients with classical S-T segment elevation, Lead aV_F displayed diagnostic Q waves as judged by the criteria of Myers in three, and Goldberger in three. Eighteen cases had negative T waves in Leads II, III, and/or aV_F that were 1 millimeter or less in five, and greater than 1 millimeter in the remaining thirteen.

DISCUSSION

The QRS vectors represent the summation of innumerable electromotive forces generated by depolarization of the ventricular myocardium. Since the over-all vector is the resultant of many forces, it is altered whenever the magnitude and/or direction of the component electrical forces are altered. Thus, when a large fraction of myocardium is rendered electrically inert by myocardial infarction, or for other reasons, there is a loss of the electromotive forces normally contributed by the involved area. That is, the QRSsÊ loop is displaced away from the lesion. These abnormal vectors can be observed in two or more planar projections.

In the present series of inferior myocardial infarction, abnormal superiorly oriented forces occurred in all cases during the initial stage of ventricular depolarization. This abnormality involved magnitude, direction, and duration; the normal values of these measurements depend on angle α of the maximal vector in the frontal plane (Table I). Since this study was confined to isolated posterior myocardial infarction, the diagnostic signs discussed do not necessarily apply to all posterior wall myocardial infarcts. Although the cases in this series were selected, among other reasons, because the initial forces displayed the above abnormalities, total experience in this laboratory establishes these criteria as the most useful in the vectorcardiographic diagnosis of inferior myocardial infarction. All observations to date have revealed the presence of these diagnostic criteria without exception in patients whose electrocardiograms display diagnostic signs of inferior myocardial infarction. Although the measurement of the initial forces in rare instances of left ventricular hypertrophy also exceed the normal, though to a slight degree, they are invariably counterclockwisely inscribed. Also, in pulmonary embolism, the initial forces may resemble those in inferior myocardial infarction, but the differentiation can be made on the basis of other features.

The value of the vectorcardiogram in the diagnosis of inferior myocardial infarction is further demonstrated by the many cases of undoubted myocardial infarction in which the vectorcardiographic diagnosis is unequivocal, while the electrocardiographic findings are of dubious or no significance. Furthermore, our limited autopsy experience has not disclosed a single instance of false diagnosis of inferior myocardial infarction, using the vectorcardiographic criteria discussed above.

In addition to the abnormal magnitude and duration of the initial forces there occurred other signs of diagnostic value: the large sweep of the initial forces, their clockwise inscription, the bizarre morphologic features of the body

and terminal appendage, and their slow inscription. The latter are probably diagnostic of intraventricular block, which is a frequent complication of inferior myocardial infarction.[7]

As noted above, many measurements (Figs. 1 to 3) exceeded the normal: the width and posterior displacement of the body, and the posterior and superior displacement of the appendage. These features, however, are also found in left ventricular hypertrophy, and are not characteristic of inferior myocardial infarct. Indeed, left ventricular hypertrophy was present in twenty-four of the thirty patients in this series. X-ray evidence of left chamber enlargement was noted in all but one with the above-mentioned abnormal measurements.

One of the most valuable findings in this study is the demonstration of diagnostic signs of inferior myocardial infarction in cases in which an initial R in aV_F is present in the electrocardiogram. Although the vectors which are represented in the electrocardiogram by an initial R wave were inferiorly oriented, as in the normal vectorcardiogram, the ensuing superior forces were abnormal and diagnostic of inferior myocardial infarction. Others have pointed out that an initial R wave in aV_F is often present in inferior myocardial infarct and conceals the electrocardiographic diagnosis of the lesion; the latter was proved at autopsy. They further pointed out that this masking of the signs of inferior myocardial infarction occurs when the electrical position of the heart is horizontal, usually in association with left ventricular hypertrophy. The patients in this present series, whose electrocardiograms duplicated the above features, i.e., initial R in aV_F, horizontal electrical position of the heart, and left ventricular hypertrophy, had vectorcardiograms which indicated the diagnosis of inferior myocardial infarction as outlined above. Whether the occurrence of an R in aV_F in inferior myocardial infarction means that the septum is not involved could not be determined in this series; the two autopsied patients whose electrocardiograms displayed initial R waves did not have septal involvement at autopsy.

The most characteristic abnormality of the T loop was its displacement in the negative quadrants in the sagittal and frontal planes. The electrocardiograms in these cases displayed characteristic T waves.

CONCLUSION

1. The vectorcardiogram in thirty cases of inferior myocardial infarction has been analyzed.

2. Morphologic and quantitative features of diagnostic value have been described.

SUMMARIO IN INTERLINGUA

Vectocardiogrammas (a systema de referentia trihedral) es describite in trenta casos de infarcimento myocardial inferior. Le methodo vecto-analytic que esseva usate in iste serie pote esser applicate a vectocardiogrammas obtenite per non importa qual systema de referential.

Le resultatos indica qualitative e quantitative deviationes ab le vectocardiogramma normal. Nos ha comparate iste constatationes con le electrocardio-

grammas que esseva prendite al mesme tempore como le vectocardiogrammas e crede poter stipular un possibile superioritate del vectocardiogramma super le electrocardiogramma in le diagnose de infarcimento myocardial inferior.

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TRANSPOSITION OF THE AORTA AND LEVOPOSITION OF THE PULMONARY ARTERY

(TAUSSIG-BING SYNDROME)

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THE identification in 1949 by H. B. Taussig and R. J. Bing[1] of the clinical, laboratory, and pathologic picture of cases of transposition of the aorta and levoposition of the pulmonary artery (Taussig-Bing Syndrome) has paved the way for subsequent reports[2-5] on this anomaly.

In both cases to be presented here the clinical picture was already suggestive; in one of them the confirmation of the diagnosis was given by the angiocardiographic examination and, in the other, by the catheterization data.

CASE REPORTS

CASE 1.—A 6-year-old boy has been under observation in our department since 1950. A heart lesion and cyanosis have been observed since he was 2 months old. Cyanosis has persisted since then. He never needed to squat and his capacity for effort has been moderately limited, although he has been able to attend school and he can bicycle. He has had frequent episodes of bronchitis.

The patient was born of a normal pregnancy and no history of viral infection could be elicited from his mother. He is an alert, well-developed, and markedly cyanotic boy, 1.18 meters in height and weighing 19.1 kilograms. There is marked clubbing and cyanosis in the four extremities. Blood pressure is 95/65 mm. Hg. Femoral arteries are normally palpable. Cardiac rhythm is regular. P_2 is markedly accentuated. There are no murmurs.

He has been examined yearly in our department without any appreciable change in the clinical data.

The roentgenogram (Fig. 1) shows a moderately enlarged and normally placed heart, with bulging of the left middle segment and marked increase in the pulmonary vascularity, although of normal pulsation.

The electrocardiogram (Fig. 2) reveals a regular sinus rhythm with marked right axis deviation. The P waves are peaked and of increased amplitude, and the P-R interval is 0.16 second. In V_{3R}, V_E, and V_1, the QRS complex is formed by a high and unnotched R wave. In V_5 and V_6, the R wave is higher than the S wave. The electrocardiographic diagnosis is right auricular and ventricular hypertrophy.

Hemoglobin is 18.2 Gm. per cent.

Catheterization of the heart (Table I) was done in 1950. We were unable to catheterize any arterial vessel. Pressures were recorded with a saline manometer. Oxygen saturation was 61 and 69 per cent, respectively, in two samples of the right ventricle, and 65 per cent in the radial artery.

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Ear oxymetry recorded a basal reading of 60 to 64 per cent, which increased to 75 per cent with respiration of oxygen, and efforts brought it down to 53 per cent.

An angiocardiogram (Fig. 3) was done, and in the first and second plates, a simultaneous opacification of a small and distinctly contrasted aorta and a faintly contrasted pulmonary artery

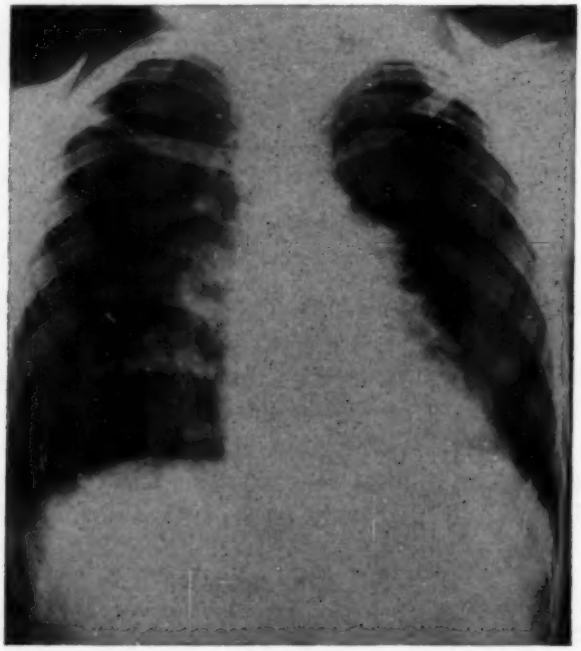


Fig. 1.—Radiography of Case 1.

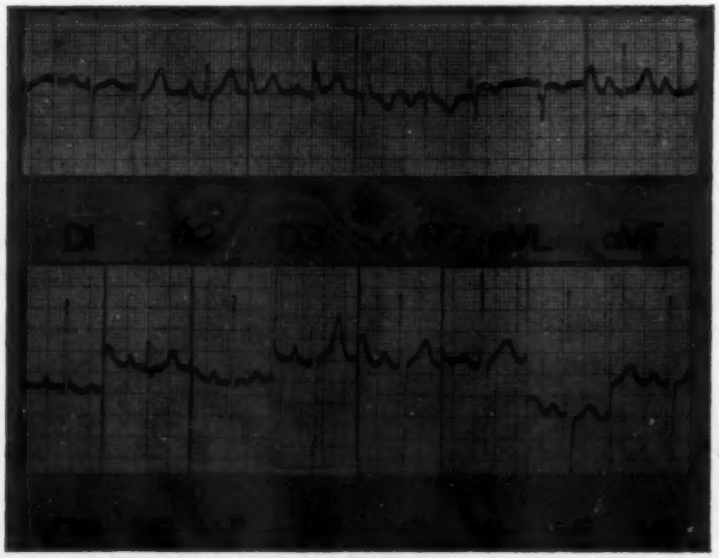
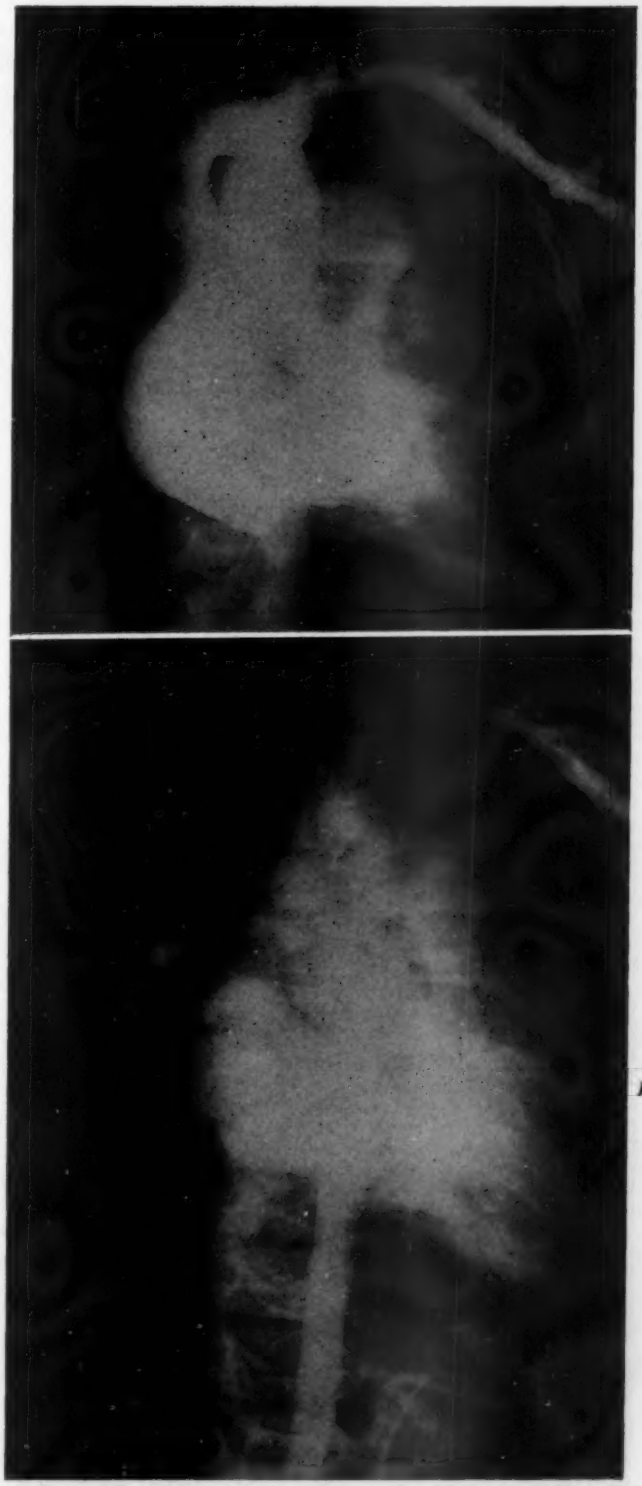


Fig. 2.—Electrocardiogram of Case 1.

are seen, while only the right side chambers are opacified. In the third and fourth plates, with left auricular and ventricular opacification, the aorta is not contrasted, although the opacification of the pulmonary artery persists. In all the plates, the contrast medium could be seen in both lung fields.



A.

B.

Fig. 3.—*A, B, C, D*, the four plates obtained during the angiocardiography.

C.

D.

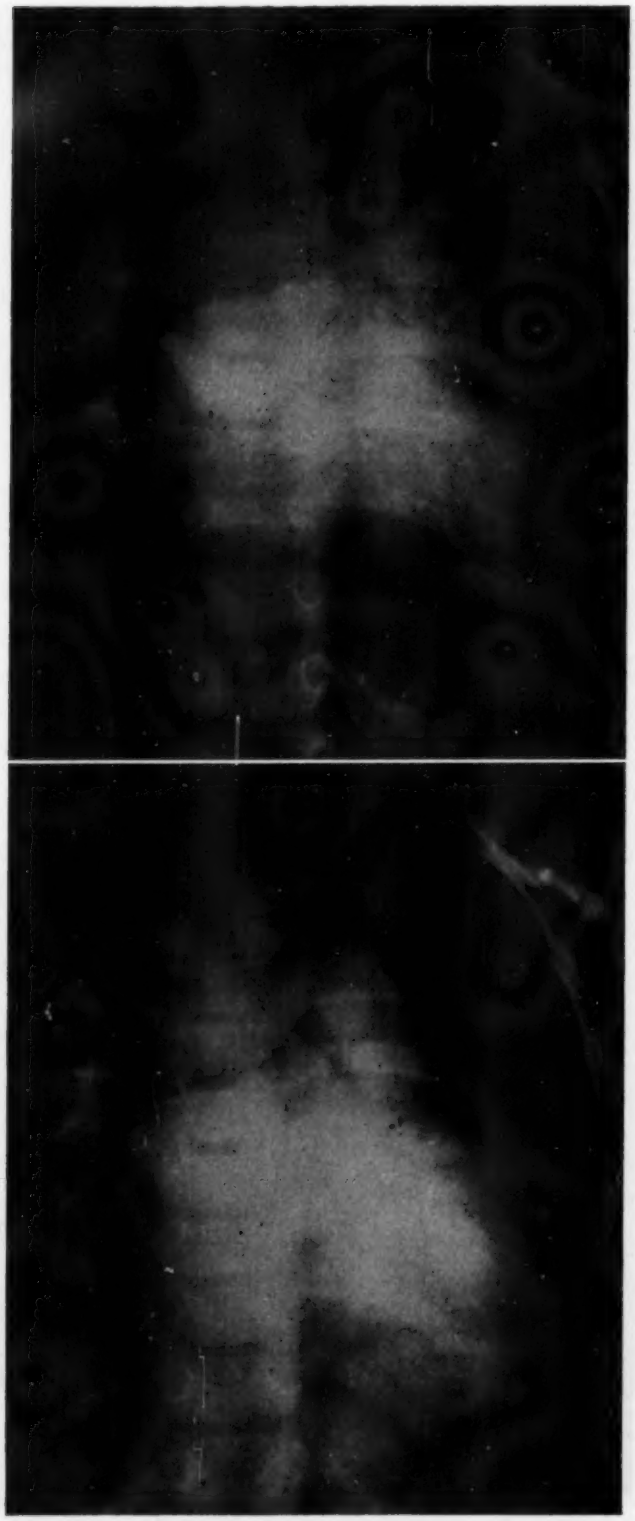


Fig. 3.—Cont'd. *(For legend see preceding page.)*

The intense opacification of the aorta in the dextroangiocardiogram while the pulmonary arteries, although opacified, are less so, and the absence of aortic opacification during the levo-angiocardiogram, were interpreted as due to the existance of a transposed aorta and a levoposed pulmonary artery.

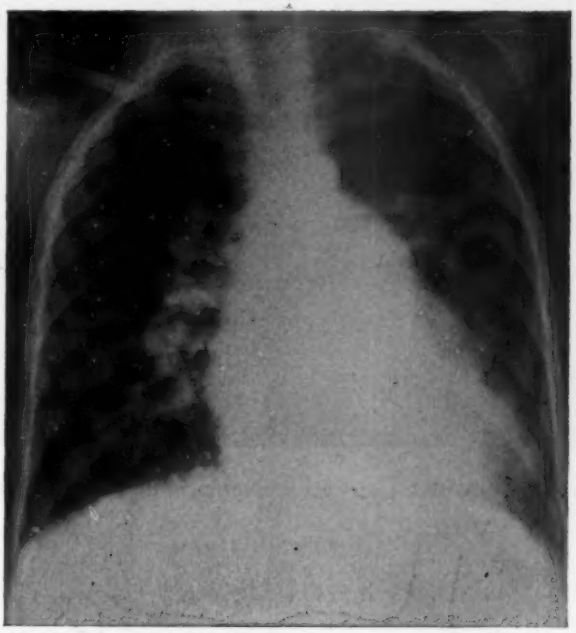


Fig. 4.—Radiography of Case 2.

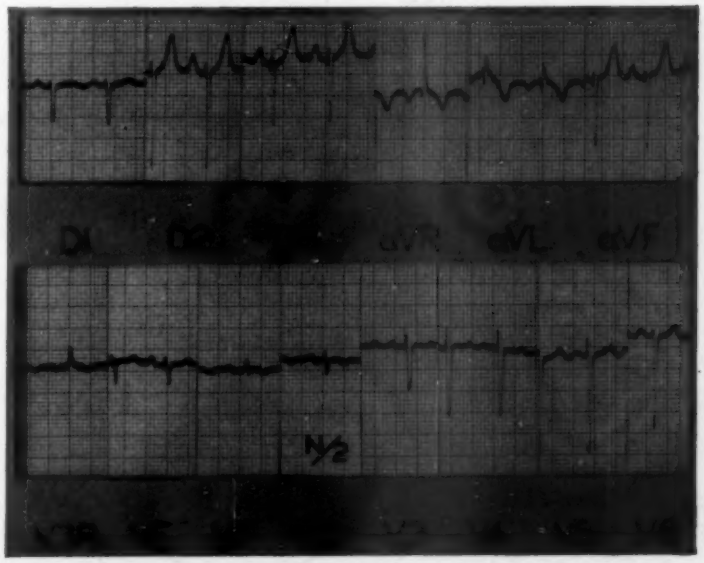


Fig. 5.—Electrocardiogram of Case 2.

CASE 2.—A 5-year-old boy has had cyansosis since his first week of life. He had one episode of faintness with increased cyanosis while crying. He never needed to squat and has had frequent respiratory infections. He is moderately incapacitated although still able to play. He is an underdeveloped boy, with marked cyanosis and clubbing of the four extremities. He is 98 cm.

in height and weighs 14 kilograms. Femoral arteries are normal and blood pressure is 80/68 mm. Hg. Cardiac rhythm is regular. P_2 is markedly accentuated and reduplicated. No murmurs are heard.

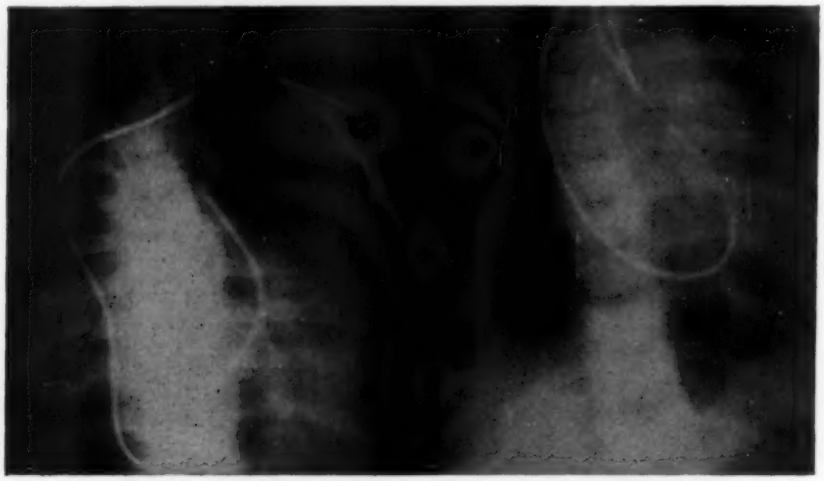


Fig. 6.—Radiography made during the catheterization of the pulmonary artery and the aorta.

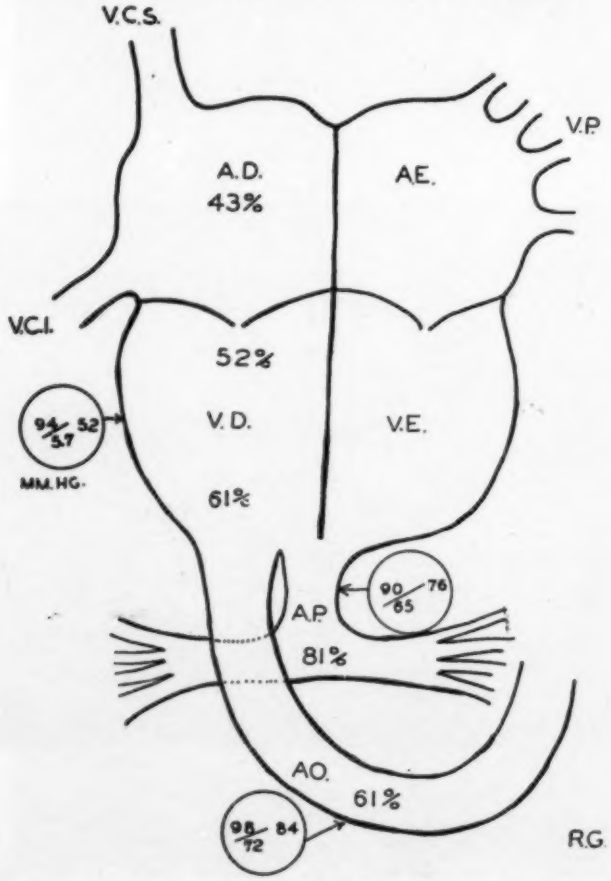


Fig. 7.—Schema of the heart with the oxygen saturations and pressures obtained in Case 2. Inside the circles are the systolic, diastolic, and mean pressures in mm. Hg.

The roentgenogram (Fig. 4) shows a moderate cardiac enlargement with a convexity of the left middle segment. Pulmonary arteries are greatly increased in size with only slight increase in pulsation.

The electrocardiogram (Fig. 5) shows an extreme grade of right axis deviation, with deep S waves in Leads I, II, III, and aV_F. The P waves are peaked and of increased amplitude in Leads II and III. The QRS complex in V_1 is formed by a notched R wave and is predominantly negative in V_6. The electrocardiographic diagnosis in this case was also right auricular and ventricular hypertrophy.

Hemoglobin is 17 Gm. per cent.

In the catheterization of the heart, both the aorta and the pulmonary arteries were entered (Fig. 6). The systolic pressure was roughly the same in both vessels and in the right ventricle. The oxygen saturation was the same in the aorta and in the right ventricle (61 per cent), and definitely greater in the pulmonary artery (81 per cent). Oxygen saturation was greater in the proximal side of the right ventricle than in the right auricle, and still greater in the distal side of the right ventricle, near the aorta (Fig. 7).

TABLE I

	PLACE	OXYGEN		PRESSURE (CM. H_2O)		
		VOL. C.C. %	SATURATION %			
FIRST CASE	Superior vena cava	12.2	48	0–4		
	Right auricle	13.5	54			
	Right ventricle	17.2	69	56–58		
	Femoral artery	16.2	65			
				PRESSURE (MM. HG.)		
				SYSTOLIC	MEAN	DIASTOLIC
SECOND CASE	Right auricle	9.55	43			
	Right ventricle proximal	11.56	52	94	52	5.7
	distal	13.55	61			
	Pulmonary artery	18.06	81	90	76	65
	Aorta	13.55	61	98	84	72

COMMENTS

In both patients, the clinical data pointed to the diagnosis of a well-tolerated congenital heart lesion with early evidence of cyanosis and increased circulation in the lungs. The absence of murmurs was against the possibility of a stenotic lesion.

In Case 1, the catheterization data were inconclusive, although the similitude of the oxygen saturation in the right ventricle and in the radial artery were in favor of a dextroposed or transposed aorta. The angiocardiogram showed not only the transposition of the aorta, well visualized in the dextro-angiocardiogram, but, also, the levoposition of the pulmonary artery, well visualized in both phases of the angiocardiogram. The lesser opacification of the pulmonary artery, compared with the aorta, was interpreted as due to the dilution

of the contrast medium in this vessel by the simultaneous arrival of blood from the unopacified ventricle, and the absence of aortic opacification during the levo-angiocardiogram, as due to the fact that the aorta did not receive blood from the left ventricle.

In Case 2, the catheterization was entirely conclusive, the data obtained confirmed the clinical suspicion, already aroused in this case, of the existence of a Taussig-Bing Syndrome. The catheterization of both vessels from the right ventricle with the same systolic pressure in those three regions, plus greater blood oxygenation in the pulmonary artery than in the aorta, could only be explained by a transposition of the aorta and a levoposition of the pulmonary artery.

The clinical picture was strikingly similar in both patients, including the absence of murmurs. The differential diagnosis with Eisenmenger complex was based not only on the early evidence of cyanosis, but also on the data of greater oxygen saturation in the pulmonary artery than in the aorta (Case 2) and on the angiocardiographic aspect showing that the aorta was contrasted only from the right ventricle, while the pulmonary artery was contrasted from both vessels (Case 1).

The continuous experimental work on transposition gives us hope that similar cases will be helped by surgery in the future.

SUMMARY

We present two patients with the clinical diagnosis of transposition of the aorta and levoposition of the pulmonary artery (Taussig-Bing Syndrome).

In both patients there was a clinical picture of a cyanotic congenital heart lesion with increased circulation in the lungs. In one patient the diagnosis was confirmed by the angiocardiographic picture, and in the other by the catheterization data.

SUMMARIO IN INTERLINGUA

Le autores presenta duo patientes con le diagnose clinic de transposition del aorta e levoposition del arteria pulmonar (syndrome de Taussig-Bing).

In ambe patientes il habeva un configuration clinic de cyanotic lesion cardiac congenite con augmento del circulation in le pulmones. In un del patientes le diagnose esseva confirmate per observationes angiocardiographic, in le altere per datos de catheterisation.

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CARDIAC ARRHYTHMIAS ASSOCIATED WITH PROTOVERATRINE

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RECENT experience with the use of protoveratrine as a depressor agent at the Peter Bent Brigham Hospital records the production of cardiac arrhythmias other than simple sinus bradycardia on nine occasions in six patients. The predominant effect of this drug in this study was the slowing of the auricular pacemaker. Other effects which were produced are probably secondary or compensatory to this depression of the sinoauricular node. In two cases, in addition, there was some degree of atrioventricular block, and in one instance delayed atrioventricular conduction presented as an isolated finding.

Protoveratrine,† a purified crystalline derivative of *Veratrum album*, produces both hypotension and bradycardia. Pharmacologic studies[1] have demonstrated that this drug activates a normal vasodepressor reflex pathway which arises in the heart, lungs, and carotid sinus and which follows an afferent course to the central nervous system through the vagus nerves. The efferent fibers, functioning as cardiodecelerators, traverse the vagus once again, ending in the sinoauricular and atrioventricular nodes of the heart; the effects produced at these loci can be prevented or abolished in most instances by the use of atropine. The efferent pathway for the peripheral vasodilatation which is, in part, responsible for the depressor response is a neurogenic one whose course is unknown at the present time. Its effects are not blocked by atropine. There is evidence[2] that part of the hypotensive effect of protoveratrine is due to direct stimulation of the central nervous system.

Several authors have noted the development of cardiac arrhythmias in their clinical trials of protoveratrine, but there are few illustrations documenting these observations in the available literature. In their early studies of this drug Meilman and Krayer[3] observed certain cardiac changes other than bradycardia. In four of eight patients with a flat or inverted T_1 and a pattern of left axis deviation, the T waves reverted to upright during the acute periods of hypo-

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†Veralba, a mixture of protoveratrine A and B, used in this study, was kindly supplied by Dr. Carl Bunde of Pitman-Moore Company.

tension induced by intravenous administration of the drug. They also encountered arrhythmias in ten patients on twenty-two occasions in the course of 168 trials. The abberations noted were described as first degree heart block, nodal rhythm, ventricular extrasystoles, bigeminy, and Wenckebach phenomenon. The arrhythmias were of short duration and intermittent, and were prevented or abolished by the use of atropine. Elek and associates[4] studied electrocardiographic changes in eighteen patients who received a mixture of the alkaloids of *Veratrum viride* intravenously and noted three instances of arrhythmia, including transient nodal rhythm, transient ventricular premature beats, and second degree atrioventricular block with ventricular premature beats changing to complete atrioventricular dissociation. Wilbrandt[5] recorded the development of ventricular premature beats in one case and nodal rhythm in another. Black and Lyons[6] have recently reported and illustrated a case in which an inadvertant overdosage of oral protoveratrine produced atrioventricular dissociation resulting from increased ventricular automaticity and associated with occasional ventricular capture. This mechanism lasted longer than twelve hours and was unaffected by atropinization.

The patients described in the present report received their protoveratrine by both oral and intramuscular routes. The arrhythmias occurred either during the initial period of dosage regulation in the hospital or during the ambulant course of chronic treatment.

CASE REPORTS

CASE 1.—R. H. (9G782), a 23-year-old white man with chronic glomerulonephritis, had developed a precipitous rise of blood pressure to levels around 210/135 mm. Hg, congestive heart failure, and papilledema in the five weeks prior to his admission to the Peter Bent Brigham Hospital on Dec. 13, 1954. Digitalization had failed to control his symptoms. The electrocardiogram on admission (Fig. 1) revealed only sinus tachycardia. On December 15 he received two doses of protoveratrine intramuscularly, 0.20 and 0.25 mg. respectively, without notable effect on his blood pressure. The following day he was given a single injection of 0.3 mg. at noon, at which time his blood pressure was 190/118 mm. Hg. One hour later when the patient complained of substernal burning and nausea he was found to have a blood pressure of 160/100 mm. Hg and a pulse of about 70 with coupling. An electrocardiogram (Fig. 1, center strips) showed the development of sinus bradycardia with first degree A-V block (P-R = 0.28 second) and ventricular escape beats giving rise to an alternating mechanism of "conducted" and "idioventricular" beats. The rate of each pacemaker was 32, the resultant rate of the heart being 64. Atropine sulfate, 0.3 mg. administered subcutaneously, resulted in relief of symptoms in about twenty minutes, at which time the blood pressure was recorded as 180/120 mm. Hg, and the pulse became regular at 80 per minute. The electrocardiogram (Fig. 1, bottom strips) showed reversion to normal sinus rhythm. At 1:30 p.m. the blood pressure was 200/135 mm. Hg, pulse 80. Ten minutes later the blood pressure was 200/140 mm. Hg, pulse was 90 and regular, and the electrocardiogram showed no further change.

The same evening protoveratrine was reinstituted at a dosage level of 0.25 mg. intramuscularly given with atropine 0.2 mg. There was seemingly some response to this dosage as casual blood pressure readings in the next twenty-four hours were recorded as low as 140/80 mm. Hg with a pulse rate of 50 per minute. A single tracing taken on December 17 (Fig. 2) showed the development of partial A-V dissociation with idioventricular rhythm and periodic ventricular capture. A follow-up tracing of December 23 (Fig. 2, bottom strip) showed normal sinus rhythm despite continued administration of protoveratrine, 0.25 mg. intramuscularly, every eight to twelve hours.

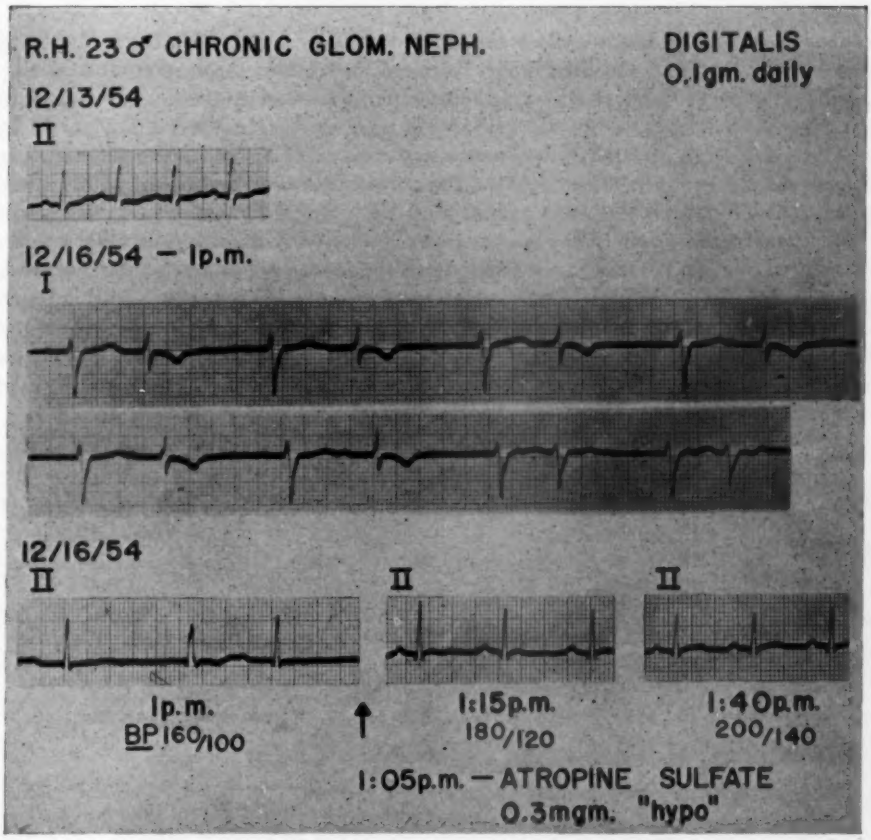

Fig. 1.—The upper strip Dec. 13, 1954, before protoveratrine shows sinus tachycardia. The electrocardiogram taken at 1 p.m. on December 16 followed an intramuscular injection of protoveratrine at 12 noon. There is sinus bradycardia with first degree A-V block (P-R=0.28 sec.) and ventricular escape beats resulting in an alternating mechanism of conducted and "idioventricular" beats. (The last two complexes in the first line of the continuous strip are reproduced as the first two complexes of the second line.) The lower three strips show effect of atropine in abolishing this disturbance.

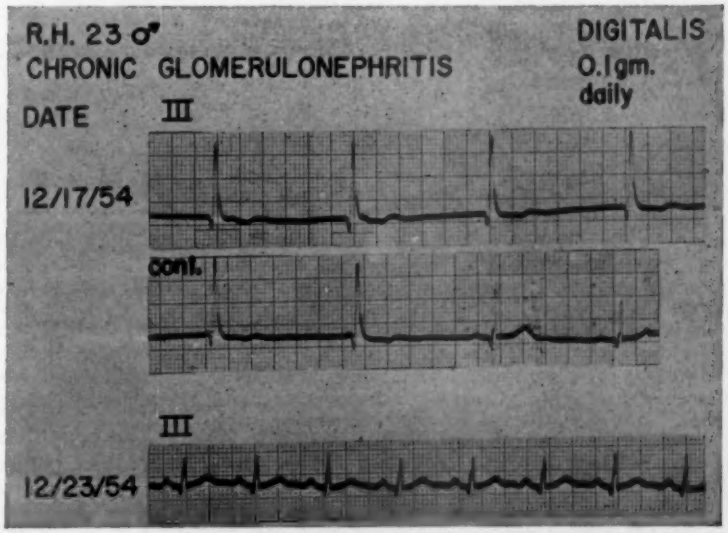

Fig. 2.—The continuous tracing recorded on Dec. 17, 1954, was taken while the patient was receiving protoveratrine 0.25 mg. intramuscularly, accompanied by atropine sulfate 0.2 mg. subcutaneously every 4 to 6 hours. It shows partial A-V dissociation and idioventricular rhythm, and periodic ventricular capture. The follow-up tracing on *12/23/54* reveals normal sinus rhythm, despite continued administration of the drug.

The drug was then discontinued for the several days of preparation for and recovery from renal homotransplantation. On December 29 protoveratrine was reinstituted and the dosage schedule was varied over the next few days because of substernal oppression which followed each successive dose of the drug. On Jan. 1, 1955, he received his protoveratrine partly by intramuscular route, 0.25 mg., and partly by mouth, 0.6 mg., at 2:30 p.m., preceded one hour earlier by 0.3 mg. of atropine. At 3:30 p.m. he vomited three times and complained of substernal burning. At 5 p.m. his blood pressure was 146/90 mm. Hg and a slight irregularity was noted in the pulse. The electrocardiogram (Fig. 3, upper two strips) showed varying P-R intervals with occasional sinus arrest and ectopic ventricular beats. He was given another 0.4 mg. of atropine hypodermically. Fifteen minutes later his electrocardiogram (Fig. 3, third tracing) returned to normal sinus rhythm except for an occasional nodal escape with a rate of 60. Over the course of the next few days the patient's protoveratrine was discontinued because of spontaneous regression of the level of the blood pressure. Subsequent electrocardiograms (Fig. 3, bottom strip) showed no arrhythmias.

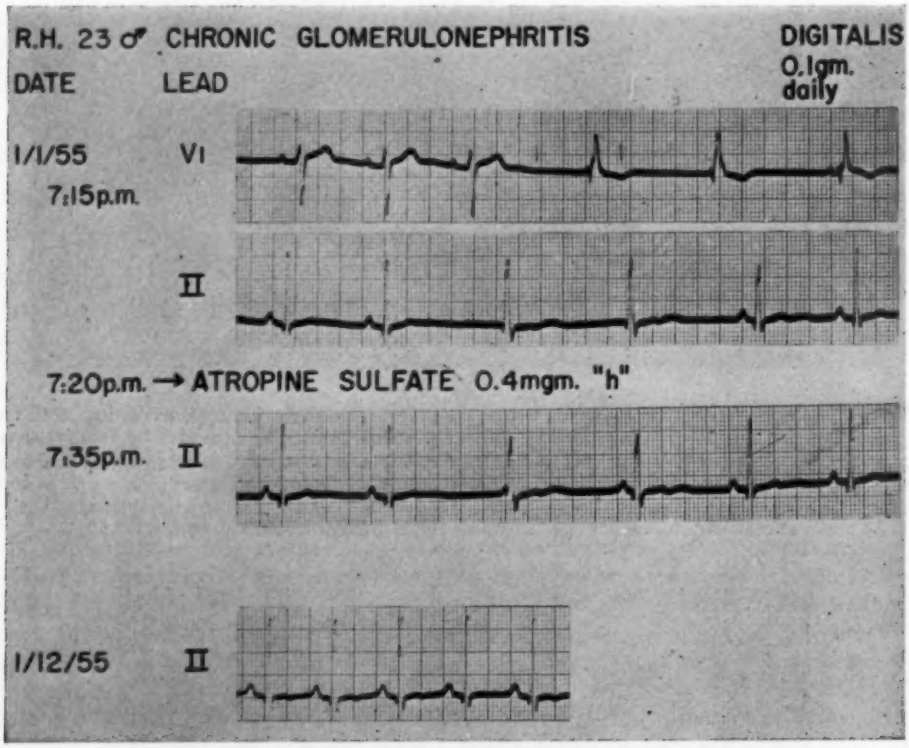

Fig. 3.—A third episode of cardiac arrhythmia in the same patient depicted in Figs. 1 and 2. The upper two strips show a varying P-R interval with occasional sinus arrest and the appearance of "idioventricular" beats. The third strip shows almost complete abolition of sinus inhibition following atropine; the third beat is a nodal escape. The final strip shows return of regular sinus rhythm following cessation of protoveratrine.

Summary.—A 23-year-old man had developed severe hypertension and congestive heart failure due to chronic glomerulonephritis. He was treated with depressor therapy while being maintained on digitalis leaf. On three occasions thereafter he developed disturbances of cardiac conduction. In two of these episodes treatment with atropine resulted in immediate reversion toward normal.

CASE 2.—S. M. (5G494), a 49-year-old white man, was admitted to the Peter Bent Brigham Hospital for treatment of hypertension of recent onset. His initial electrocardiogram on Feb. 21,

1954 (Fig. 4, upper strip), showed a pattern of left ventricular hypertrophy with a normal sinus rhythm, a rate of 76 per minute and a P-R interval of 0.19 second. Treatment was undertaken with oral protoveratrine in graduated amounts. On March 2 he received 1.7 mg. of the drug at 8 a.m., immediately after breakfast. His blood pressure, starting at 220/130 mm. Hg, fell gradually over the next four hours until at noon, when the patient was complaining of weakness, fatigue, and dizziness, the pressure reached a low of 120/80 mm. Hg. Electrocardiogram (Fig. 4, second, third, and fourth strips) taken at this time showed apparent first degree A-V block with sinus rhythm giving way, during waning of the auricular rate, to A-V dissociation. The rate of the ventricles during dissociation was 48 and during the period of apparent conduction was 51. This mechanism was interpreted as representing a combination of partial A-V dissociation and first degree A-V block. Treatment consisted merely of bedrest with head-down position; the blood pressure gradually rose, reaching 200/110 mm. Hg by 9 p.m. The heart rate also returned to normal.

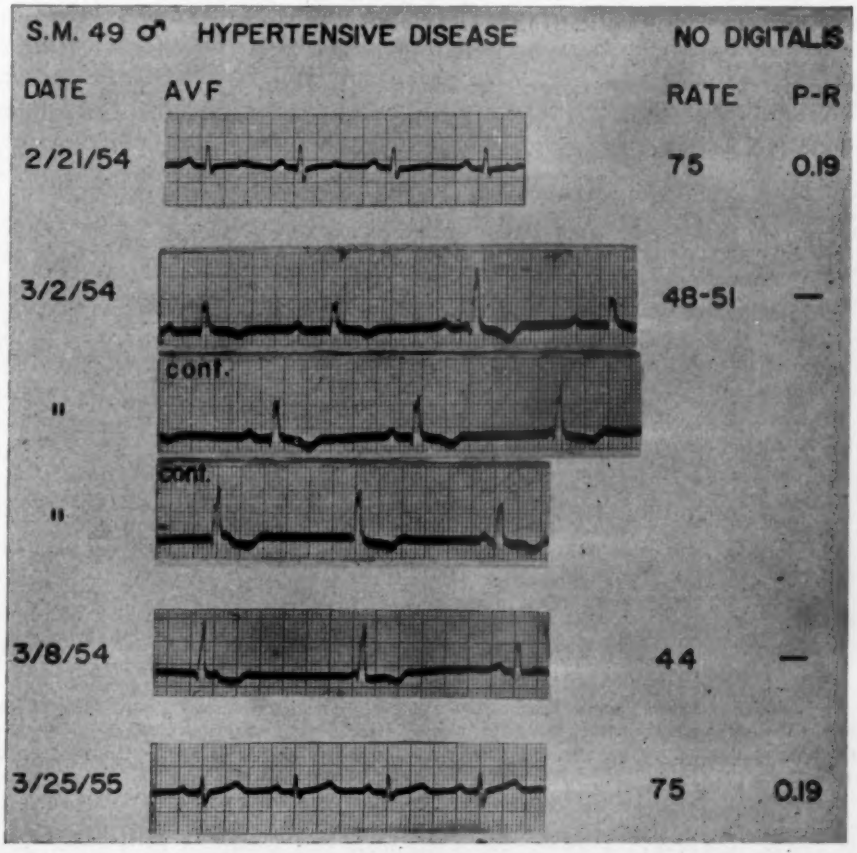

Fig. 4.—Normal sinus rhythm is present in the top strip prior to protoveratrine. The continuous tracing of March 2, 1954, taken four hours after an oral dose of 1.7 mg. of protoveratrine shows first degree A-V block with sinus rhythm, giving way during waning of the atrial rate to A-V dissociation. A second episode of arrhythmia occurring on *3/8/54*, two hours after an oral dose of 1.4 mg. of protoveratrine, is shown in the fifth strip. The mechanism is similar to that of the previous episode, except that the difference between conducted and nonconducted ventricular complexes is more evident. The bottom strip showing normal sinus rhythm was taken four months after discontinuance of protoveratrine.

Further regulation of the dosage of protoveratrine was undertaken. Six days after the above episode, the patient received 1.4 mg. of the drug after breakfast, this same dose having been moderately effective the several days previously. He developed vomiting, perspiration, and faintness two hours later. Blood pressure was 120/70 mm. Hg and pulse rate was 44 per

minute. The electrocardiogram (Fig. 4, fifth strip) showed a phenomenon similar to that seen previously with a striking demonstration of the difference in configuration between the ventricular complexes of the captured and of the nonconducted beats. There was again a gradual return of pressure and rise in pulse rate over a five-hour period.

Subsequently the patient was maintained on protoveratrine on an outpatient basis for a period of eight months and, though the drug proved to be moderately effective in reducing his blood pressure, no further disturbances of the cardiac mechanism were again recognized. An electrocardiogram taken March 25, 1955 (Fig. 4, bottom strip), when the patient was no longer receiving this drug showed a normal sinus rhythm.

Summary.—A 49-year-old man with moderately severe hypertensive disease was placed on routine protoveratrine therapy. During the initial adjustments of dosage, the patient achieved excellent depressor response and a marked bradycardia on two occasions. Electrocardiograms showed a combination of partial atrioventricular dissociation and first degree atrioventricular block which reverted to normal without specific treatment. The patient received no digitalis during the course of this hospitalization.

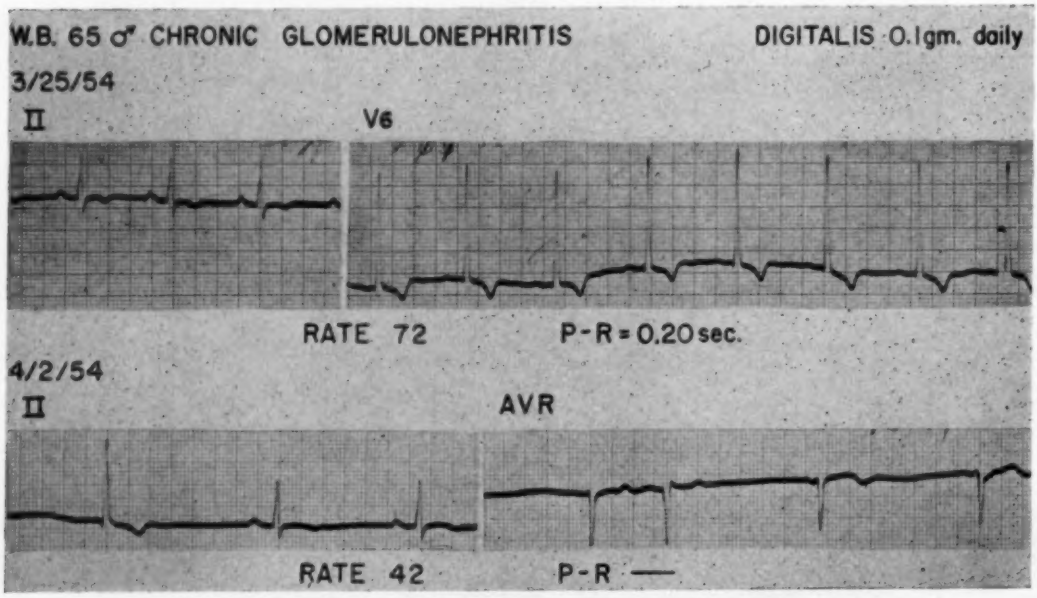

Fig. 5.—The upper tracing shows normal sinus rhythm prior to protoveratrine. The electrocardiogram shown in the bottom strip was recorded two hours after 1.0 mg. of protoveratrine by mouth. There was sinus bradycardia with periodic auricular standstill and ventricular escapes. Coupled rhythm was noted at times.

CASE 3.—W. B. (J4984), a 65-year-old white man, was known to have glomerulonephritis eighteen years prior to his admission to the Peter Bent Brigham Hospital in March, 1954. His blood pressure ranged between 185 and 220 mm. Hg systolic and 95 to 120 mm. diastolic. The patient was noted to have developed left ventricular failure, inadequately controlled by digitalis. The admission electrocardiogram (Fig. 5, upper strip) showed normal sinus rhythm and left ventricular hypertrophy. On April 2, shortly after breakfast, he received 1.0 mg. of protoveratrine orally. Two hours later he complained of nausea and of a substernal oppressive sensation. His blood pressure was found to have fallen to 158/70 mm. Hg and his heart rate was slow and, for the most part, regular, with only an occasional irregularity. An electrocardiogram (Fig. 5, bottom strip) now showed the development of sinus bradycardia (rate 42) with periodic atrial standstill, ventricular escape, and occasional variation in the ventricular complexes of the conducted beats. Coupled rhythm was present at times. Several hours later, without specific

therapy, the patient's symptoms disappeared; however, his blood pressure remained around 160 to 170/80 to 90 mm. Hg and the pulse rate about 60 the rest of that day.

For the next seven months, until the time of the patient's death, he was maintained on slightly smaller doses of protoveratrine. On no other occasions were there any objective evidences of protoveratrine intoxication relating to the cardiac mechanism.

Summary.—A 65-year-old man, being treated with digitalis for congestive heart failure, developed a severe disturbance in his cardiac mechanism after his first oral dose of protoveratrine. He had no recurrence of this difficulty despite continued use of the drug in slightly smaller dosage for a period of about seven months.

CASE 4.—E. M. (5G131), a 30-year-old white man, was admitted to the Peter Bent Bringham Hospital in December, 1953, for treatment of far-advanced chronic glomerulonephritis with severe hypertension and congestive heart failure. After digitalization with digoxin, he was started on protoveratrine, of which he received gradually increasing doses every four to six hours intramuscularly. It was found that 0.35 mg. at four hourly intervals maintained his blood pressure around 190/100 mm. Hg, a level considered to represent an adequate reduction when contrasted with the control levels of 270/160 mm. Hg.

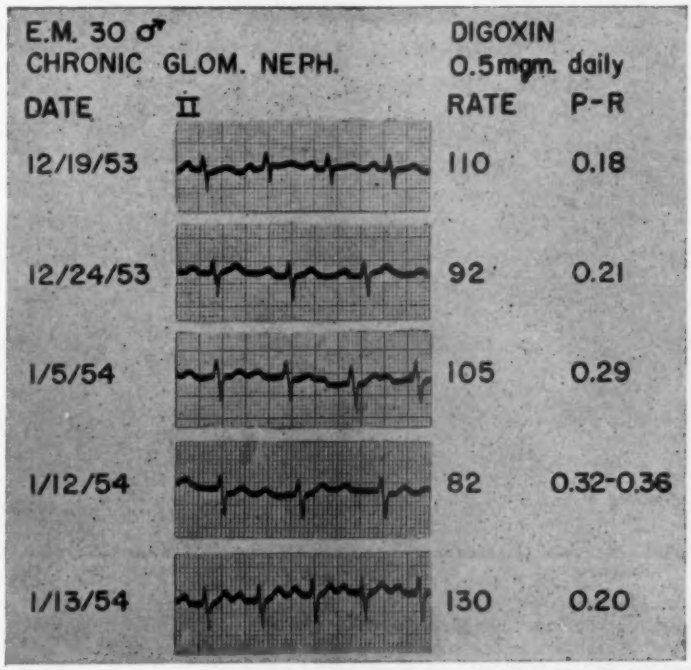

Fig. 6.—Upper strip is control tracing before protoveratrine Dec. 19, 1953. Second, third, and fourth strips, recorded while the patient was receiving protoveratrine intramuscularly, show first degree A-V block. The final strip Jan. 13, 1954, was taken ten hours after the preceding one, with no protoveratrine in the interval. The patient received no specific treatment for the block, except discontinuance of the drug.

The initial electrocardiogram taken shortly after admission (Fig. 6, first strip) showed a normal sinus rhythm with a P-R interval of 0.18 second and a rate of 110 per minute. Two subsequent readings (Fig. 6, second and third strips) in the course of the next three weeks revealed evidence of first degree A-V block with P-R intervals varying from 0.21 to 0.29 second. A tracing taken on Jan. 12, 1954 (Fig. 6, fourth strip), after a short run of irregular beats had been heard by a house physician, revealed a P-R interval varying from 0.32 to 0.36 second, but no evidence of cardiac irregularity in the recorded strip. Because of the possibility that the conduction defect might be due to protoveratrine, the drug was omitted for two doses. At the end of this time, ten

hours after the last previous dose of 0.35 mg. intramuscularly, the P-R interval had shortened to 0.20 second (Fig. 6, final strip). Thereafter, despite more cautious use of protoveratrine, P-R intervals of 0.24 and 0.32 second were recorded on subsequent tracings.

Summary.—A 30-year-old white man was suffering from severe and rapidly advancing hypertension secondary to chronic glomerulonephritis. Protoveratrine was administered intramuscularly at four hourly intervals with the early development of first degree atrioventricular block. This pattern was completely reversed on one occasion by the discontinuance of the drug for a ten-hour period. The patient was receiving digoxin during this course.

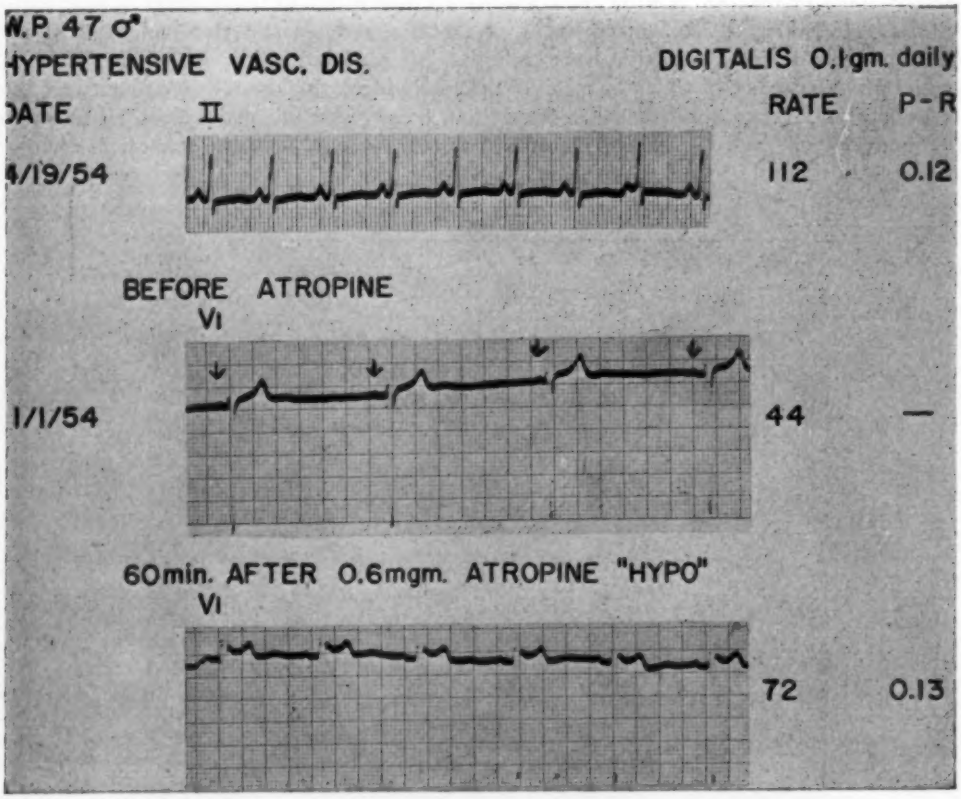

Fig. 7.—Upper strip is a control tracing prior to protoveratrine. The second strip shows sinus arrhythmia and sinus bradycardia with partial A-V dissociation and nodal rhythm, occurring during the chronic ambulant use of protoveratrine. Sixty minutes after administration of atropine (lower strip) the rate had increased to 72 and normal sinus rhythm had returned.

CASE 5.—W. P. (L4104), a 47-year-old Negro, was admitted to the hospital in April, 1954, for treatment of hypertension and congestive heart failure. He was treated with digitalis and with protoveratrine, receiving of the latter 1.0 mg. orally after breakfast and 0.4 mg. after lunch and supper. He was discharged from the hospital on this regimen, having exhibited no difficulties during the initial period of dosage regulation. His initial electrocardiogram showed normal sinus rhythm (Fig. 7, upper strip).

In the course of chronic ambulant treatment over the next six months, he was maintained on a similar dose of protoveratrine without ill-effect, his pulse rate being recorded between 44 and 52 beats per minute at all times. On Nov. 1, 1954, he had developed a slower pulse rate (40 per minute) without resultant symptoms. An electrocardiogram at this time (Fig. 7, second strip) showed sinus arrhythmia and sinus bradycardia with partial A-V dissociation and nodal rhythm. He was given atropine sulfate, 0.6 mg., subcutaneously. One hour later his pulse

was regular at 72, and the electrocardiogram (Fig. 7, bottom strip) showed reversion to normal sinus rhythm. Thereafter, he was given no further protoveratrine.

Summary.—A 47-year-old Negro tolerated protoveratrine orally for about six months, at which time he was found to have a marked sinus bradycardia and partial atrioventricular dissociation. Atropine blocked the arrhymia. The patient had been maintained on digitalis throughout this time.

CASE 6.—M. R. (8D622) was a 56-year-old white woman with hypertension and hypertensive headaches. In July, 1952, she was first started on protoveratrine, the dosage ranging between 0.7 and 1.0 mg. each morning and about 0.6 mg. each afternoon. She was followed at frequent intervals and noted to have an average pulse rate of about 72, though a single reading of 56 was recorded. An occasional electrocardiogram (Fig. 8, first strip) showed normal sinus rhythm.

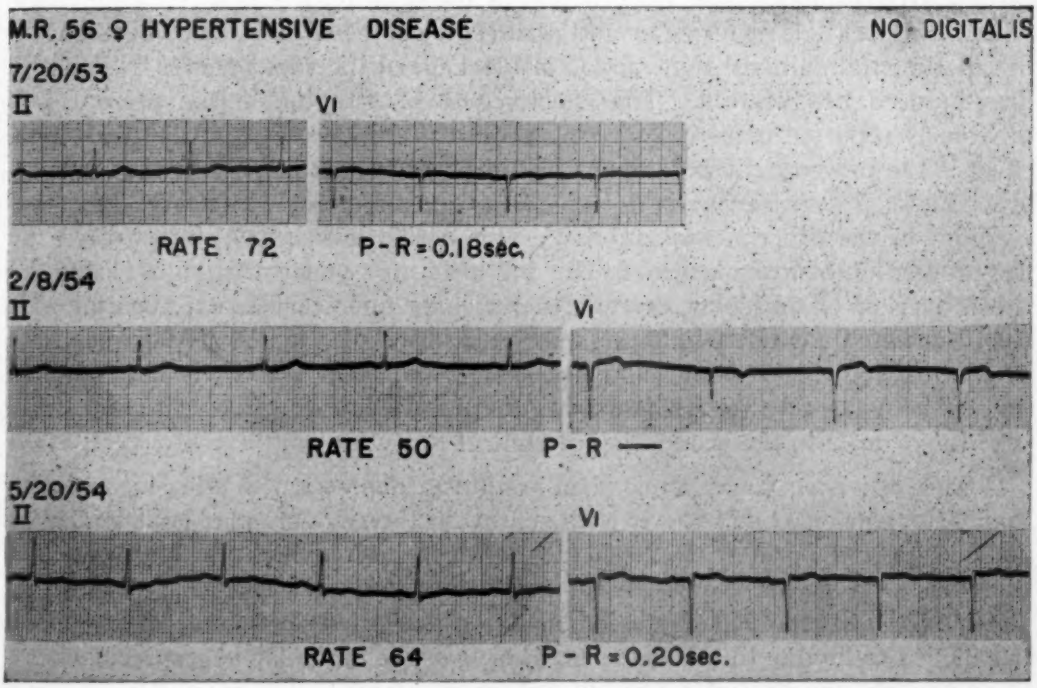

Fig. 8.—The first strip shows normal sinus rhythm taken after the patient had been on protoveratrine treatment for about one year. The tracing of Feb. 8, 1954, was recorded during an episode of hypotension associated with nausea, weakness, numbness in the fingers, and substernal oppression. It shows sinus bradycardia with wandering of the pacemaker and changing configuration of the ventricular complexes. The bottom strip shows normal rhythm despite continued use of protoveratrine in slightly reduced doses.

On Feb. 8, 1954, she appeared in the clinic complaining of severe weakness, nausea, burning in the back, numbness in the fingers, and a substernal sense of oppression; she stated that she had experienced similar episodes on previous occasions. Her blood pressure was 90/60 mm. Hg, and her pulse regular at a rate of 50. An electrocardiogram (Fig. 8, middle strip) showed sinus bradycardia with a slight wandering of the pacemaker, the P-R intervals varying from 0.14 to 0.18 second, and the complexes following the longer P-R intervals differing slightly in appearance from those following the shorter P-R intervals. The patient was placed in the supine position and given a hypodermic injection of 0.3 mg. of atropine sulfate. Thirty minutes later her blood pressure was 100/60 mm. Hg, at sixty minutes 160/110, and by ninety minutes 170/120. The pulse rate rose during this period.

The patient has been treated with protoveratrine in slightly reduced doses since this time, and has manifested no additional reactions of the type noted (Fig. 8, bottom strip). She has not required digitalis at any time.

Summary.—A 56-year-old woman had been taking protoveratrine for a period of over one and one-half years when her only recorded attack of cardiac arrhythmia was noted. There had been no change in the treatment schedule for many months preceding the episode. She has been continued on the drug in reduced doses without further complication. The patient has never taken digitalis. It cannot be stated with certainty that protoveratrine caused this arrhythmia, as the evidence here is less convincing than in the preceding cases. However, it was the clinical opinion of those who observed her at the time that this episode was due to overdosage with protoveratrine.

DISCUSSION

There are two possible mechanisms by which protoveratrine may produce cardiac arrhythmias. The vagal action of the drug results in direct cholinergic stimulation of the sinoauricular and atrioventricular nodes. It has been shown in experimental animals[1] that section or blockage of the vagus nerves will abolish drug-induced bradycardia. The effectiveness of atropine in the present and previously reported cases in reversing the arrhythmias suggests that this vagal effect is the primary cause of the arrhythmias in the clinical situation. On the other hand, protoveratrine is known to have a direct toxic effect on the myocardium in the experimental animal. This action has been demonstrated[1] by the production of irregularities in the dog heart in a concentration of 1:106, by the induction of auricular asystole, ventricular tachycardia, or fibrillation in the denervated dog heart-lung preparation, and by initation of A-V dissociation, premature ventricular beats, and ventricular standstill in systole when applied in increasing doses to the isolated frog heart. It is doubtful that this mechanism is of importance in the production of clinical arrhythmias.

This excessive vagal tonus then results in depression of the sinoauricular and atrioventricular nodes. It is the effect on the sinoauricular node which we consider to be the primary factor in most of these cases, evident in the appearance of sinus bradycardia, sinus arrest, and wandering pacemaker. In addition, the partial and complete atrioventricular dissociation in several of the cases is believed to be due to this same depression of the auricular pacemaker, whereupon the phenomenon of ventricular escape becomes apparent; the mechanism is not considered an enhancement of the nodal or ventricular pacemaker. In the sense of Ashman[7] then, these are arrhythmias by "default" rather than by "usurpation." However, it is implicit in the production of first degree atrioventricular block in three of the cases, that depression of the A-V node also plays a role in the described arrhythmias.

A word as to the distinction between atrioventricular *block* and atrioventricular *dissociation* is in order. Until recently the terms were used interchangeably. Currently, "block" is used in the sense of a barrier between the atria and ventricles, so that atrioventricular conduction time is delayed ("first-degree" block, "latent" block, as in Case 4, Fig. 6) or some of the atrial beats are unable to penetrate to the ventricles ("second-degree" or "partial" block, as described by Meilman and Krayer[8]) or none of the beats penetrate to the ventricles ("complete" heart block). In this condition the atrial rate exceeds the ventricular rate. "Dissociation" denotes a condition in which the atrioventricular node or an "idioventricular" focus escape from atrial domination by virtue, either of

excessive slowing of the atrial pacemaker ("rhythm by default," as in most of the present cases), or by increased automaticity of the ventricles ("rhythm by usurpation," as in the case of Black and Lyons[6]). Whether by default or usurpation, the ventricular rate exceeds the atrial rate. Atrioventricular conduction is still unimpaired so that occasional ventricular "capture"* may occur; in this case the mechanism is referred to as "partial atrioventricular dissociation." At times, as in the present Case 1 (Fig. 1, middle strips) and Case 2 (Fig. 4), there may be a combination of atrioventricular block and dissociation.

The only previously published electrocardiograms of protoveratrine toxicity available to the authors have been those of Black and Lyons.[6] In these tracings there is a pattern similar to that seen in several of the patients here presented, that is, incomplete atrioventricular dissociation with an occasional conducted beat. It is of interest, however, that these tracings reveal a more rapid auricular rate than was seen in the present series. A possible explanation of this disparity lies in the fact that atropine had been administered to this patient prior to the first recorded electrocardiogram; a direct toxic action on the myocardium may be an alternate explanation.

Structurally protoveratrine is similar to the cardiac glycosides and pharmacodynamically both of these groups of drugs owe at least part of their effectiveness to vagal stimulation. It has been claimed by some authors that patients who are digitalized develop cardiac arrhythmias on smaller doses of protoveratrine than those not being treated with digitalis.[3] However, of two groups of patients manifesting arrhythmias with the veratrum alkaloid, only four out of ten[3] patients in one series and three out of seven[8] in another series were receiving digitalis. Hoobler[9] failed to note increased toxic effects of protoveratrine given orally in his digitalized patients.

The arrhythmias described in this report have been produced by overdosage of protoveratrine rather than of digitalis. The question of whether the presence of the cardiac glycosides increases the propensity of protoveratrine toxicity is not answered by the present observations. Of the six cases, two were not receiving digitalis and one of these individuals (Case 6) developed her arrhythmia on a relatively small dose of the drug. Caution is nonetheless advised in the concomitant use of digitalis and protoveratrine.

SUMMARY

1. Six hypertensive patients receiving protoveratrine developed various forms of cardiac arrhythmias on nine occasions. These arrhythmias consisted of sinus bradycardia, sinus arrest, wandering pacemaker, first-degree atrioventricular block, and partial and complete atrioventricular dissociation. All of these mechanisms reverted to normal sinus rhythm with time or with the administration of atropine.

2. These arrhythmias are believed to result from excessive vagal stimulation by the drug, producing depression of the sinoauricular and atrioven-

*This apt designation is borrowed from the Chicago School of Pick, Langendorf, and Katz.

tricular nodes of the heart. A direct toxic effect of protoveratrine on the myocardium cannot definitely be excluded.

3. It is emphasized that protoveratrine may produce either atrioventricular block or atrioventricular dissociation, or both. Atrioventricular dissociation may occur by virtue of excessive sinus slowing and ventricular escape (default) or increased ventricular automaticity (usurpation). In the present series of cases, the effect in depressing the sinoauricular node was paramount.

4. At times these toxic effects appeared to be related to a certain critical threshold dosage of the drug; at other times, they occurred on maintenance dosage previously tolerated without toxic symptoms.

5. Digitalis preparations were being used concomitantly in four of the six patients. No definite conclusion as to the possible synergistic action of these two drugs in the production of these arrhythmias can be made from this small series of cases.

SUMMARIO IN INTERLINGUA

Nove occurrentias de arrhythmia cardiac esseva notate in sex patientes con hypertension tractate per Protoveratrina. Iste droga, que es un purificate derivato crystallin ab *Veratrum album*, exerce su effectos hypotensive in grande mesura via le nervos vage. Depression del pacemaker atrial, probabilissimemente un resultato de iste stimulation vagal, se provava un denominator commun del arrhythmias, manifeste in le production de arresto sinusal, de pacemakers migrante, e de partial e complete dissociation atrio-ventricular in le majoritate del patientes. In plus, bloco atrio-ventricular e retardation del conduction atrioventricular esseva notate in un numero de casos. Tractamento con atropina o simplemente abstention ab Protoveratrina resultava in le renormalisation de iste alterationes. Le arrhythmias esseva apparentemente producite in le majoritate del casos per quantitates critic o plus que critic del droga. Le studio non permitte le stipulation de un absolute relation inter le uso de digitalis e le apparition de arrhythmias in patientes sub tractamento depressori.

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MYOCARDIAL INFARCTION TREATED BY EARLY AMBULATION

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PROLONGED bed rest has for decades been regarded as the cornerstone of treatment of myocardial infarction. Recently, however, opinions have changed in this respect. Levine[3,4] especially has emphasized during the past ten years that recumbency is in many cases harmful to a patient who is acutely ill with cardiac disease. His "armchair treatment" has gained wide acceptance. In this treatment the patient, immediately following recovery from the state of shock, is allowed to sit in a chair, at first for a short time and later for a gradually increasing part of the day. Ambulation is usually started three to four weeks after infarction.

Still earlier ambulation is recommended by Irvin and Burgess.[2] They consider two weeks of bed rest sufficient in most cases of myocardial infarction. This should be followed by two weeks of gradual and progressive ambulation. The total length of hospitalization would thus be limited to four weeks.

Since the summer of 1952, patients with myocardial infarction at the Medical Clinic of the University of Turku have been prescribed shorter and less strict bed rest than previously. Immediately after the state of shock has subsided, the patients have been permitted to sit up in the bed. Bedside toilet privileges have also usually been allowed at an early stage. Two weeks after infarction, if no special contraindications are present, the patients have been allowed to begin ambulation. One week later they have been dismissed from the hospital. In addition to the usual medical treatment, all the patients were administered phenylindanedione as an anticoagulant.

Our experiences with this treatment during the past three years have been favorable. It is our impression that the patients have maintained their physical condition better and have regained their normal activity considerably sooner than patients under the old regimen of prolonged bed rest. The early ambulation does not appear to have been of any immediate harm to the patient. However, in order to evaluate better the results of our therapy, we have reviewed the cases of myocardial infarction treated in our clinic in the latter half of 1952, and during 1953 and 1954.

MATERIAL

During the stated period, 332 patients with definite myocardial infarction were treated in our clinic. Seventy-four patients, equivalent to 22.4 per cent of the series, died during bed rest before ambulation was started. The following survey covers the remaining 258 patients.

From the Medical Clinic of the University, Turku, Finland.
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There were seventy-four female patients (28.7 per cent). The mean age of these patients was 63 years, of the male patients 54 years, and of the total series 57 years. Using the pathologic index rate of Schnur[6] as an indication of the severity of this illness, the following distribution of cases is obtained:

Pathologic index rate	0 to 39	156 patients
Pathologic index rate	40 to 79	85 patients
Pathologic index rate	80	17 patients

The relatively low number of severe cases in our series is due to the exclusion of the patients dying during bed rest, whose pathologic index rate was high in many cases.

A distribution of the cases according to the electrocardiographic pattern showed anterior, anterolateral, or anteroseptal type in 154 cases (60.0 per cent), posterior or posterolateral type in seventy-five cases (29.0 per cent), purely lateral in five cases, and purely septal in ten cases. In the remaining fourteen cases an accurate determination of the type was not possible.

The average length of bed rest in our series was 16.2 days and the average length of hospitalization 22.6 days.

Follow-up data, based partly on later examinations or treatment at our clinic and partly on written information from the patient, or, after his death, from his family, was procured for 236 of the 258 patients, or in 91.5 per cent of the cases.

We shall review below the complications occurring during ambulation in the hospital and during the first six months after hospital.

Complications During Ambulation in Hospital.—

Sudden death: Two patients died suddenly. One of these was a 64-year-old metal worker, who in addition to myocardial infarction had cardiovascular syphilis. The bed rest in this case had lasted three weeks. After being an ambulatory patient for eighteen days he died suddenly. The other patient, a man aged 63 years, had an infarction of the septal type. His bed rest was also longer than normally (twenty-five days) and he died on the first day of ambulation.

Recidive myocardial infarction: The only case was a man, aged 59, who had a relapse of myocardial infarction after ten days of bed rest and ten days of ambulation, but recovered.

Congestive heart failure: Mild symptoms of congestive heart failure developed in five patients during ambulation.

Complications During First Month After Hospital.—

Sudden death: One case.

Recidive myocardial infarction: Twenty-one cases, seven of which ended fatally. In six cases the infarction occurred during the first week after dismissal from the clinic. Four of these patients had been hospitalized for the normal period of three weeks and the other two for a longer time (thirty-one and thirty-four days). In addition to these twenty-one cases of definite myocardial infarction, eight patients (including five women) were rehospitalized during the first month because of indefinite pains in the chest. The large proportion of women among these patients is probably attributable to psychic factors.

Complications Two to Six Months After Hospital.—

Sudden death: Ten cases.

Recidive myocardial infarction: Ten cases, one of which was fatal.

Angina pectoris: Eight patients were rehospitalized because of aggravated symptoms of angina pectoris. Two of these patients had, later, a recidive myocardial infarction.

Congestive heart failure: Heart failure of such severity developed in four patients as to demand rehospitalization.

Pulmonary infarction: One case.

Follow-Up Six Months After Myocardial Infarction.—

Ability to work: After the exclusion of the patients who died within six months from the myocardial infarction and those who had a relapse within the the same period, the postocclusion work history was obtained for 190 patients. Six months after infarction seventy-one of these patients (37.4 per cent) had returned to their former occupation and twenty-nine patients (15.3 per cent) were in lighter work than previously; the remaining patients were not working. There were forty-seven intellectual workers in the series, for whom the corresponding percentages were 68 and 11, and 143 manual laborers, with percentages of 29.7 and 19.8.

Cardiac aneurysm: A follow-up roentgenologic examination was made in forty-eight cases. The examination revealed a cardiac aneurysm in one patient only.

DISCUSSION

From the results reported above, it is apparent that no immediate hazard to the patient is associated with ambulation after a bed rest of two weeks only. No deaths occurred among the patients in our series who were allowed to start ambulation two weeks after onset of the infarction, for both of the patients who died in the hospital during ambulation had been confined to bed for a longer time. It may be mentioned for comparison that, in the series of 242 cases reported from Sweden by Eckerström,[1] which probably is best comparable with our series, there were seventeen deaths during the third week of bed rest in the hospital. The total mortality in our series during the first six months from the beginning of ambulation is also fairly small (twenty-two deaths), this figure in Eckerström's series being forty-four. It is to be observed, however, that our mortality of seventy-four deaths during two weeks of bed rest was also definitely lower than the 110 deaths in Eckerström's series.

It is interesting to note the number of recidive infarctions during the first month after dismissal from the hospital, i.e., during the fourth to seventh weeks after the acute attack. During this period there were twenty-one recidive myocardial infarctions, six of which occurred during the first week. However, the bed rest had been limited to two weeks only for four of these six patients. In regard to the severity and localization of the original infarctions, these twenty-one recidive infarctions did not differ from the rest of the series.

We have not found in the literature any suitable reports which could serve as a basis for comparison of the incidence of recidive infarctions. It seems probable, however, that the risk of recidive infarctions may have increased to some degree after dismissal of the patients from the hospital. If this increase is a true and not a seeming one, it may be due either to an incautious and sudden increase of physical activity of the patients at home, or to discontinuance of the anticoagulant therapy when the patients left the hospital.

As regards other complications, their number in our series appears to be below, rather than above normal. It is especially to be noted that a cardiac aneurysm was found in only one case in the follow-up examinations. A roentgenologic follow-up, it is true, was made of forty-eight patients only, but it also was mainly in these patients that the presence of complications was suspected.

SUMMARY

Since 1952, the bed rest in the treatment of myocardial infarction in the Medical Clinic of the University of Turku has been limited to two weeks. A report on 332 patients with myocardial infarction treated in 1952 to 1954 indicates that early ambulation was not associated with an increased hazard to the patients as regards the rate of mortality. The incidence of other complications did not appear to be higher, at least, than normally, with the exception, perhaps, of the incidence of recidive myocardial infarctions during the first month after dismissal from the hospital.

SUMMARIO IN INTERLINGUA

Depost 1952, allectamento in le tractamento de infarcimento myocardial al Clinica Medical del Universitate Turku ha essite limitate a duo septimanas. Un reporto concernente 332 patientes con infarcimento myocardial tractate ab 1952 a 1954 indica que le ambulation precoce non esseva associate con un augmento de hasardo, manifeste in un augmento del mortalitate. Le frequentia de altere complicationes non pareva exceder le norma, con le possibile exception del frequentia de recidivas de infarcimentos myocardial durante le prime mense post le dimission del patientes ab le hospital.

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ATRIAL FLUTTER DURING QUINIDINE THERAPY OF ATRIAL FIBRILLATION*

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DURING the treatment of atrial fibrillation by the use of quinidine, a stage of atrial flutter was often observed. The latter occurred both in instances that were eventually converted to regular sinus rhythm and in those that failed to do so. The frequency with which the intermediary stage of atrial flutter was noted varied, depending a great deal on how often electrocardiographic studies were performed during the course of quinidine therapy. It is the purpose of this communication to report the frequency with which atrial flutter was noted in cases of atrial fibrillation during the course of quinidine therapy, and to analyze the mechanism of atrial arrhythmias in the light of this study.

MATERIALS AND METHODS

For this study 115 patients with atrial fibrillation were included. The exact duration of the atrial fibrillation was uncertain in most instances; however, it was estimated to be from at least a few months to many years in the majority of the patients. With the exception of one, all patients had heart disease. The etiological classification of heart disease has been as follows: (1) degenerative heart disease which includes hypertensive and arteriosclerotic heart disease; (2) rheumatic heart disease; (3) syphilitic heart disease; (4) chronic cor pulmonale; and (5) thyrotoxic heart disease.

All patients with the exception of one entered the hospital in congestive heart failure, and received digitalis and other therapeutic agents as routinely employed in the treatment of congestive heart failure, including bed rest, low salt diet, mercurial diuretics, xanthine derivatives, ammonium chloride, and other measures whenever indicated. Digitalis was given throughout the course of quinidine administration.

Quinidine sulfate was administered by mouth and daily determination of quinidine blood level made according to the methods outlined in our previous publication.[1] In several patients more than one course of quinidine therapy was

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given, due either to the recurrence of the atrial fibrillation or to failure to attain successful conversion on the first occasion. If conversion to normal sinus rhythm occurred at any time, the dosage of quinidine was reduced by half the next day or two and the drug was then discontinued completely. If conversion did not occur by the end of the seventh day on an optimal dosage schedule, the drug was discontinued altogether. In all cases daily blood samples were drawn for determination of the level of quinidine in the plasma which was continued till the level reached zero on two consecutive days. In some cases several blood samples were drawn on one day if significant change in the heart rhythm or rate was noted.

All electrocardiograms were taken on the Sanborn, Cambridge, or General Electric direct-writing cardiographs and consisted of the twelve conventional leads. In the earlier period of the study, only Lead II was taken at intervals of one to three or four days during the course of quinidine therapy. In the latter period of the study, all three standard limb leads and three precordial leads, V_1, V_2, and V_4 were taken routinely, at least once a day and often several times a day whenever transient changes in the rate or rhythm were anticipated.

RESULTS

Development of Atrial Flutter.—The patients with atrial fibrillation in this study can be classified into four groups,* according to whether atrial flutter was demonstrated as atrial fibrillation was being converted with quinidine:

> Group I includes twenty-seven patients (thirty-two attempts) who developed atrial flutter during quinidine therapy with eventual conversion to sinus rhythm;
>
> Group II includes thirty-nine patients (forty-two attempts) who developed atrial flutter but failed to be converted to a sinus rhythm;
>
> Group III includes forty-five patients (fifty-eight attempts) who were converted to sinus rhythm without atrial flutter being demonstrable on the electrocardiogram; and
>
> Group IV includes ten patients (thirteen attempts) who developed neither atrial flutter nor normal sinus rhythm any time during the course of quinidine therapy.

TABLE I. FOUR GROUPS OF ATRIAL FIBRILLATORS

	SEQUENCE OF EVENTS	NO. OF TIMES	PERCENTAGE OF TOTAL
Group I	Fibrillation→flutter→sinus	32	22
Group II	Fibrillation→flutter	42	29
Group III	Fibrillation→sinus	58	40
Group IV	Fibrillation failed to be converted to either flutter or sinus	13	9
	Total	145	

*Several patients received more than one course of quinidine therapy to attempt conversion and therefore were included under more than one group.

The duration of the intermediary stage of atrial flutter demonstrated among patients in Group I varied from one to sixteen days, averaging two days.

When Group I and Group II are added together, the incidence of the occurrence of atrial flutter during treatment of atrial fibrillation with quinidine is 51 per cent. However, this study should be divided into two periods: the early

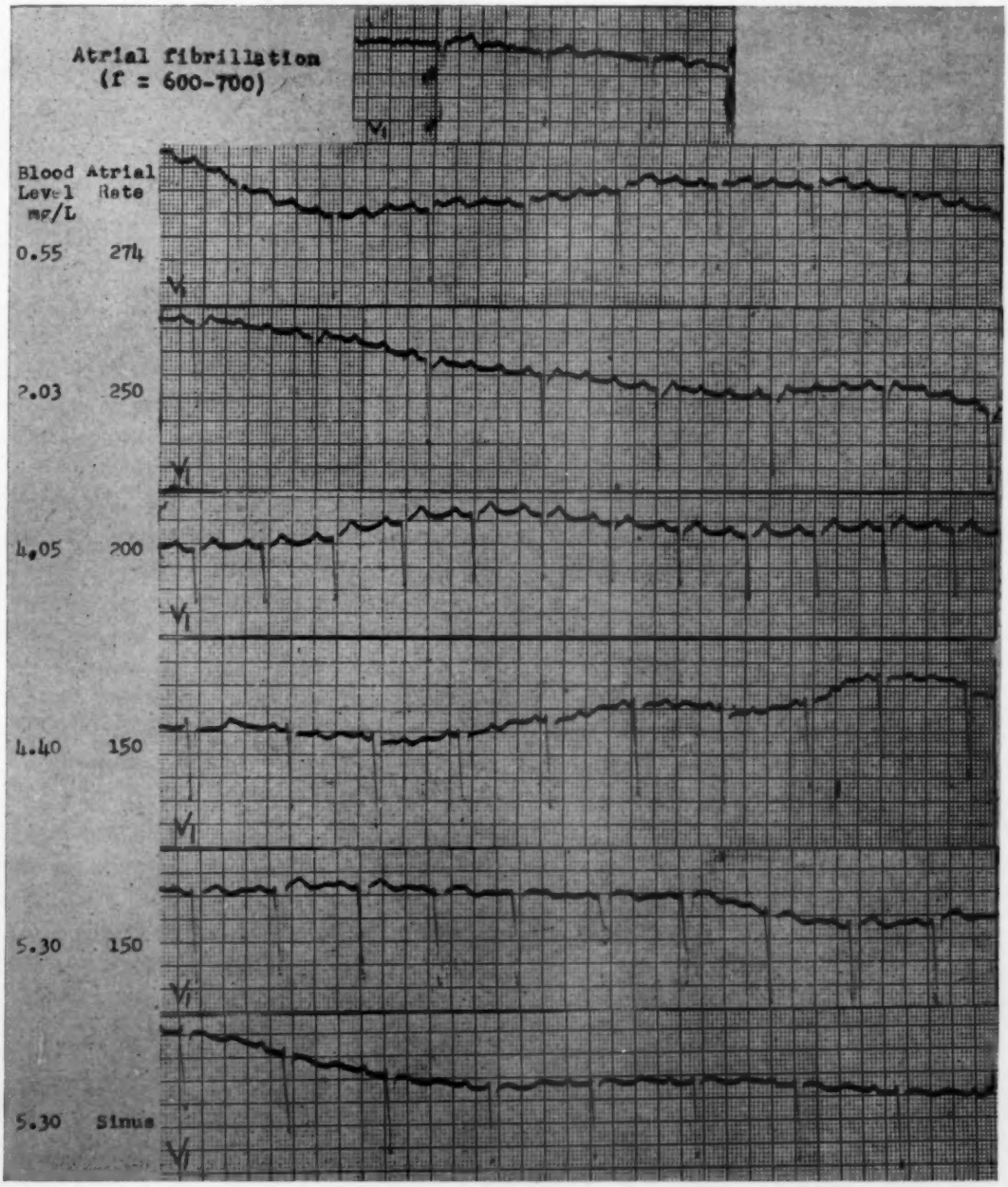

Fig. 1.—Serial tracings of Lead V_1, taken daily, of Case 36, P.V., during the course of quinidine therapy for atrial fibrillation (row 1), showing the appearance of atrial flutter with progressive slowing of the atrial rate as the blood level of quinidine rose (rows 2 to 6) before regular sinus rhythm was finally restored (row 7). Note the difficulty in differentiation between atrial flutter and atrial tachycardia as the atrial rate slowed down to 150 per minute.

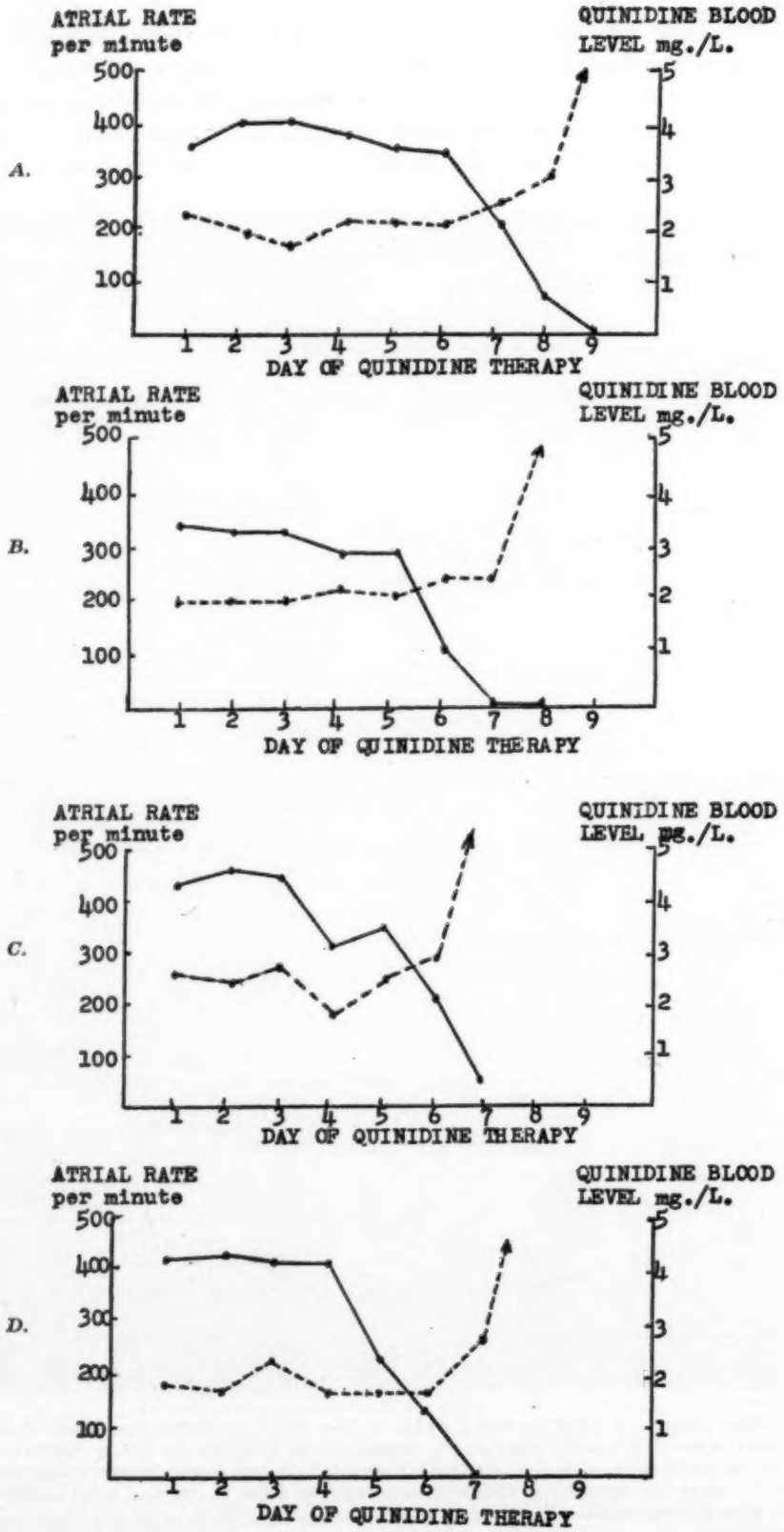

Fig. 2.—Correlation between the quinidine blood level and the effect on the atrial rate in induced atrial flutter in four patients during quinidine therapy for atrial fibrillation. In each diagram the upper curve (solid line) is the quinidine blood level in milligrams per liter and the lower curve (dotted line) atrial rate of the induced flutter. The arrowhead indicates atrial fibrillation. *A*, Case 55, J. C.; *B*, Case 59, R. Mc.; *C*, Case 45, J. W.; *D*, Case 98, P. F.

period which included thirty-five attempts at conversion with quinidine (twenty-eight cases) in which electrocardiograms were recorded at rather infrequent intervals, and the later period which included 110 attempts at conversion (eighty cases) in whom electrocardiograms were recorded daily or several times a day. By comparison we can see that almost twice as many cases were shown to exhibit the stage of atrial flutter in the later period as were in the early period (Table II).

TABLE II. DEPENDENCE OF INCIDENCE OF THE INTERMEDIARY STAGE OF ATRIAL FLUTTER ON THE FREQUENCY WITH WHICH ELECTROCARDIOGRAPHIC RECORDINGS WERE MADE

	WHEN INFREQUENT ECG'S WERE TAKEN (35 ATTEMPTS)	WHEN FREQUENT ECG'S WERE MADE (110 ATTEMPTS)
Group I	4 (11.4%)	28 (25.5%)
Group II	8 (22.8%)	34 (31%)
	Total: 34.2%	Total: 56.5%

Therefore, the actual incidence of the appearance of atrial flutter during treatment of atrial fibrillation with quinidine was definitely higher the oftener electrocardiographic observations were made.

In most of our cases that developed atrial flutter during treatment of atrial fibrillation with quinidine, the rate of atrial activity decreased proportionately as the blood level of quinidine rose before normal sinus rhythm was finally restored (Fig. 1). Such a parallelism was illustrated in Fig. 2. This parallelism between the quinidine blood level and the rate of atrial movement has also been observed by other investigators.[2-4]

Among the twenty-five relapses which occurred while the patient was still under close observation in the hopsital, twenty (80 per cent) again progressed through the stage of atrial flutter with increasing atrial rates as the blood level of quinidine declined until the rhythm was finally atrial fibrillation (Figs. 3 and 4).

A-V Conduction in Atrial Flutter.—In all the cases with quinidine-induced atrial flutter, the atrial rate varied from 354 to 120 per minute. The average rate was 188 per minute. The most usual finding was a 2:1 A-V block. In some cases with decrease of atrial rate as the blood level of quinidine rose, ventricular rate showed a "paradoxical" increase. Higher degrees of A-V block were less common, although 4:1 block was not infrequent. A 3:1 block was much less frequent, and it was frequently intermingled with 2:1 or 4:1 block.

Wenckebach phenomenon was observed fourteen times during the period of atrial flutter (Figs. 5, 6, and 7), as a result of quinidine therapy for atrial fibrillation.

One-to-one conduction occurred in induced atrial flutter during quinidine therapy four times in three patients (Fig. 7). Full digitalization was accomplished and maintained at the time the accelerated 1:1 conduction occurred in all three patients. In the patient whose electrocardiogram is illustrated in Fig. 7, the episode of 1:1 conduction was followed two hours later by the restoration of the sinus rhythm. During the two-hour period of the rapid ventricular response the patient experienced no untoward effects.

DISCUSSION

That the development of atrial flutter is a common result of quinidine therapy given for conversion of atrial fibrillation to sinus rhythm has been emphasized in the past,[5-8] and was again confirmed in this study. The frequency with which it is observed probably depends on the diligence of the observer and the frequency

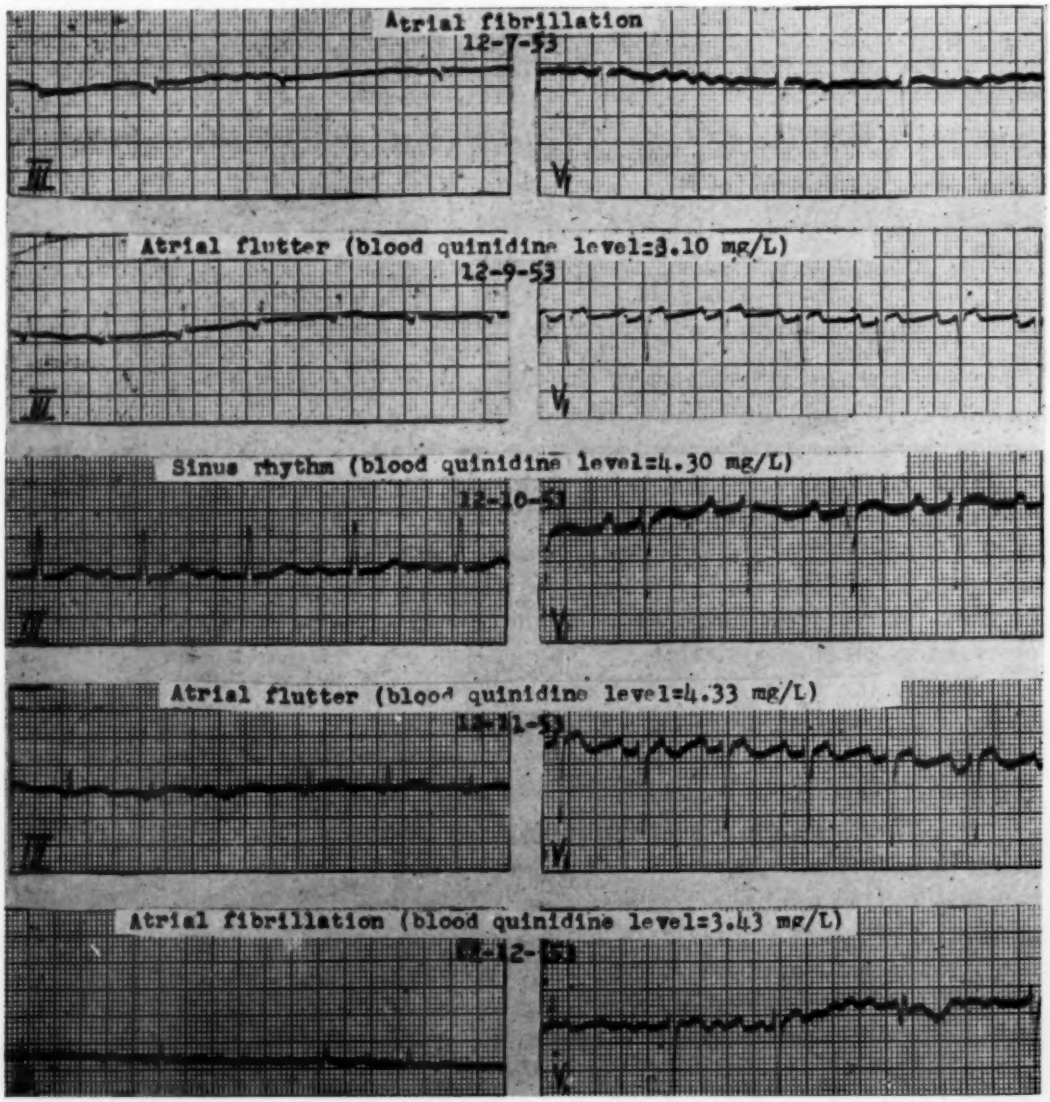

Fig. 3.—Serial tracings of Leads III and V_1 of Case 51, R.H., taken during the course of quinidine therapy, showing the transitional stage of atrial flutter as atrial fibrillation was converted to normal sinus rhythm, and again as the rhythm reverted back to atrial fibrillation while still on quinidine therapy.

with which electrocardiographic studies were performed. Goldman[6] reported the appearance of atrial flutter in 70 per cent of his cases of atrial fibrillation treated with quinidine.

The marked reduction of atrial rate with quinidine administration to 188 to 120 per minute makes the differentiation between atrial flutter and atrial

tachycardia almost impossible. Difficulty in differentiating between atrial flutter and atrial tachycardia has been described by many authors.[9-14] The separation is even more difficult when atrial tachycardia has a rate between 180 and 260 per minute and is associated with partial A-V block. In fact atrial rates between 180 and 270 per minute with varying degree of partial heart block

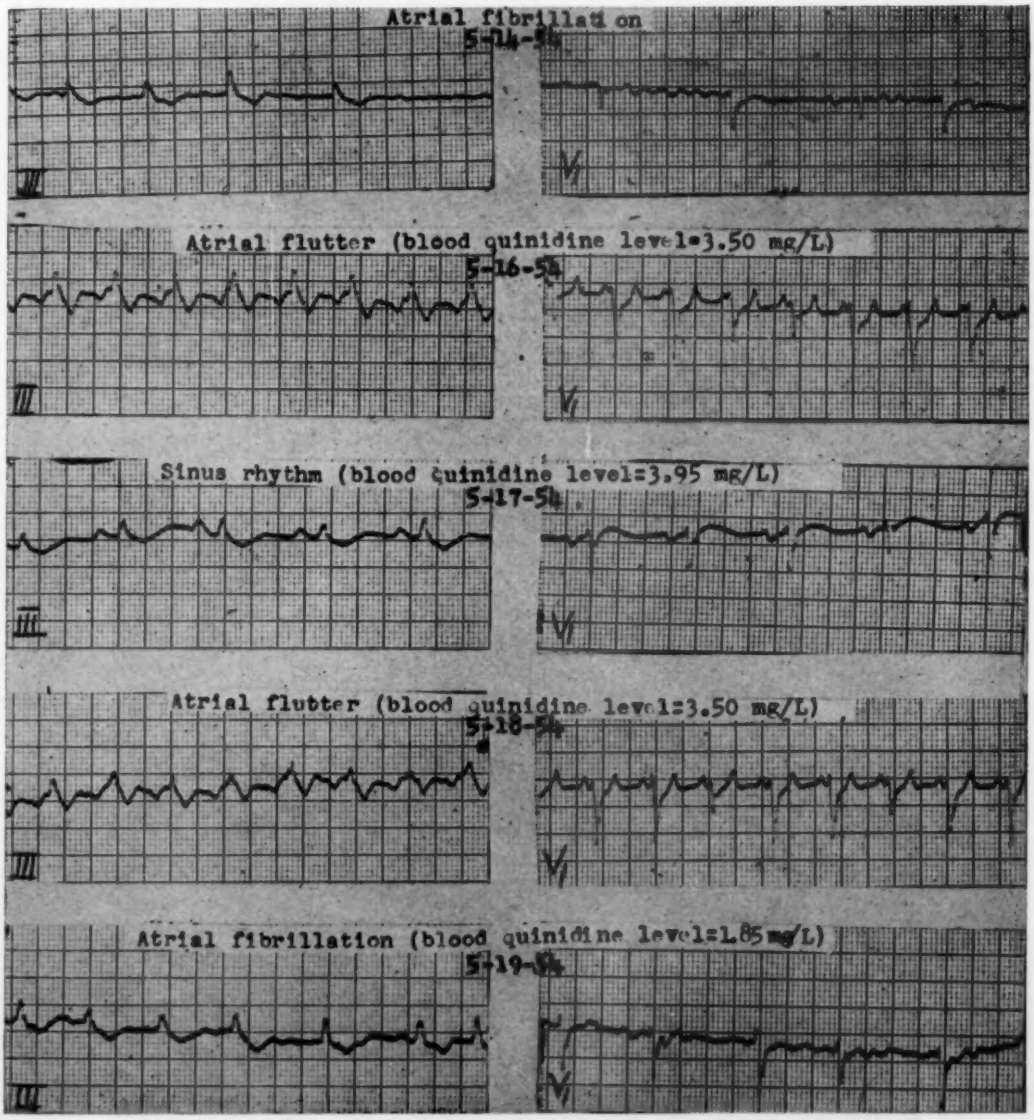

Fig. 4.—Serial tracings of Leads III and V_1 of Case 90, B.R., taken during the course of quinidine therapy, showing the transitional stage of atrial flutter as atrial fibrillation was converted to normal sinus rhythm and again as the rhythm reverted back to atrial fibrillation upon the discontinuation of quinidine.

have been interpreted by some authors as atrial flutter[10,13] and by others as atrial tachycardia.[15-17] The criteria advanced by Lewis[18] for differentiation between paroxysmal atrial tachycardia and atrial flutter are no longer appropriate when the tachycardia occurs with A-V block.[16] The most important criterion in dif-

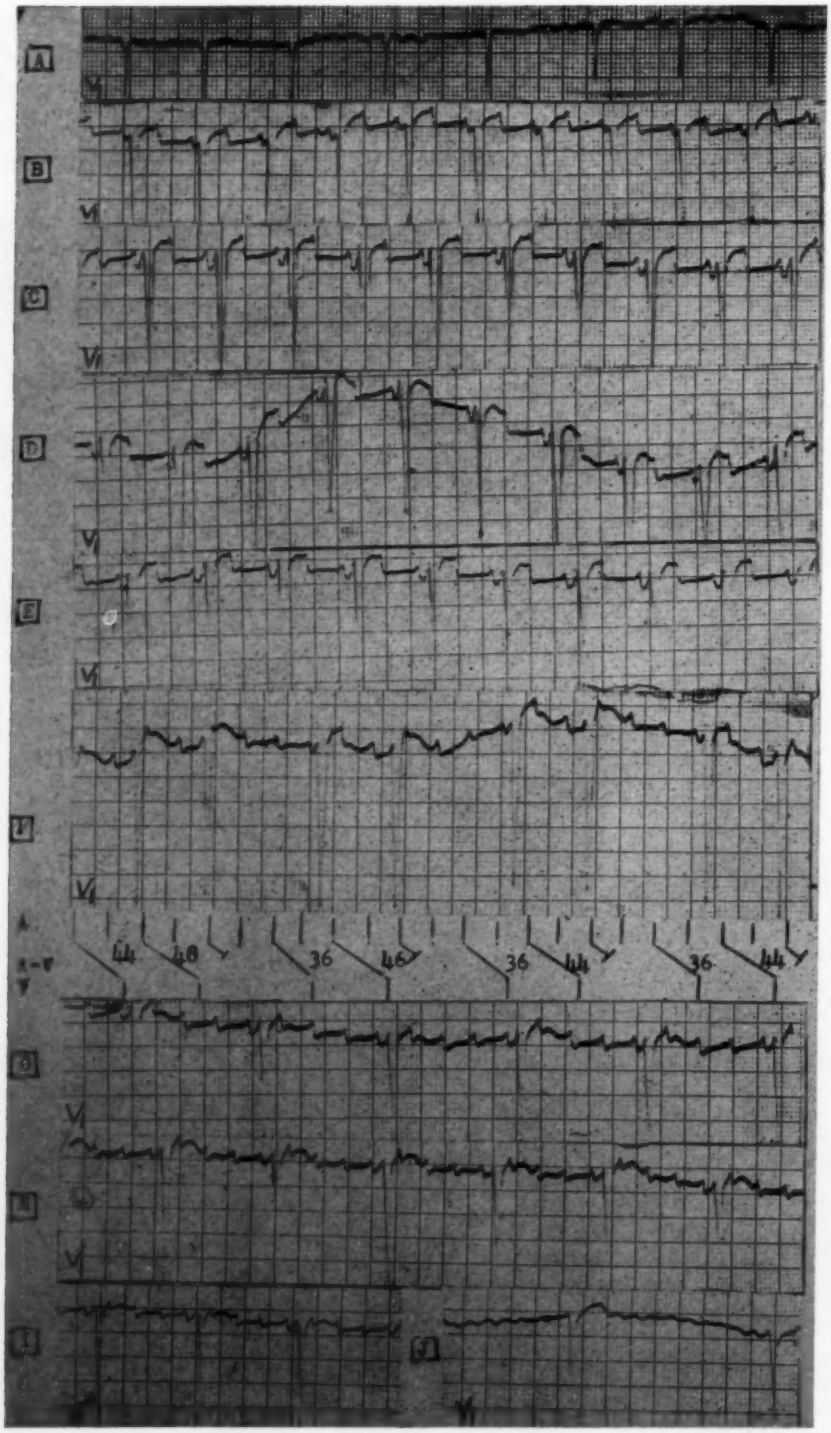

Fig. 5.—Electrocardiograms of Case 55, J.C., recorded at daily intervals, illustrating (1) the parallelism between the atrial rate and the blood level of quinidine, and (2) the occurrence of Wenckebach type of block as an intermediary stage between a lower and a higher degree of A-V block in atrial flutter resulting from quinidine therapy. *A*, Atrial fibrillation (f = 440) before quinidine therapy. *B*, Atrial flutter (f = 214) with 2:1 block; blood level = 3.6 mg. per liter. *C*, Atrial flutter (f = 200) with 2:1 block; blood level = 4.0 mg. per liter. *D*, Atrial tachycardia (a = 188) with 2:1 block; blood level = 4.1 mg. per liter. *E*, Atrial flutter (f = 214) with 2:1 block; blood level = 3.8 mg. per liter. ***(Legend continued on opposite page.)***

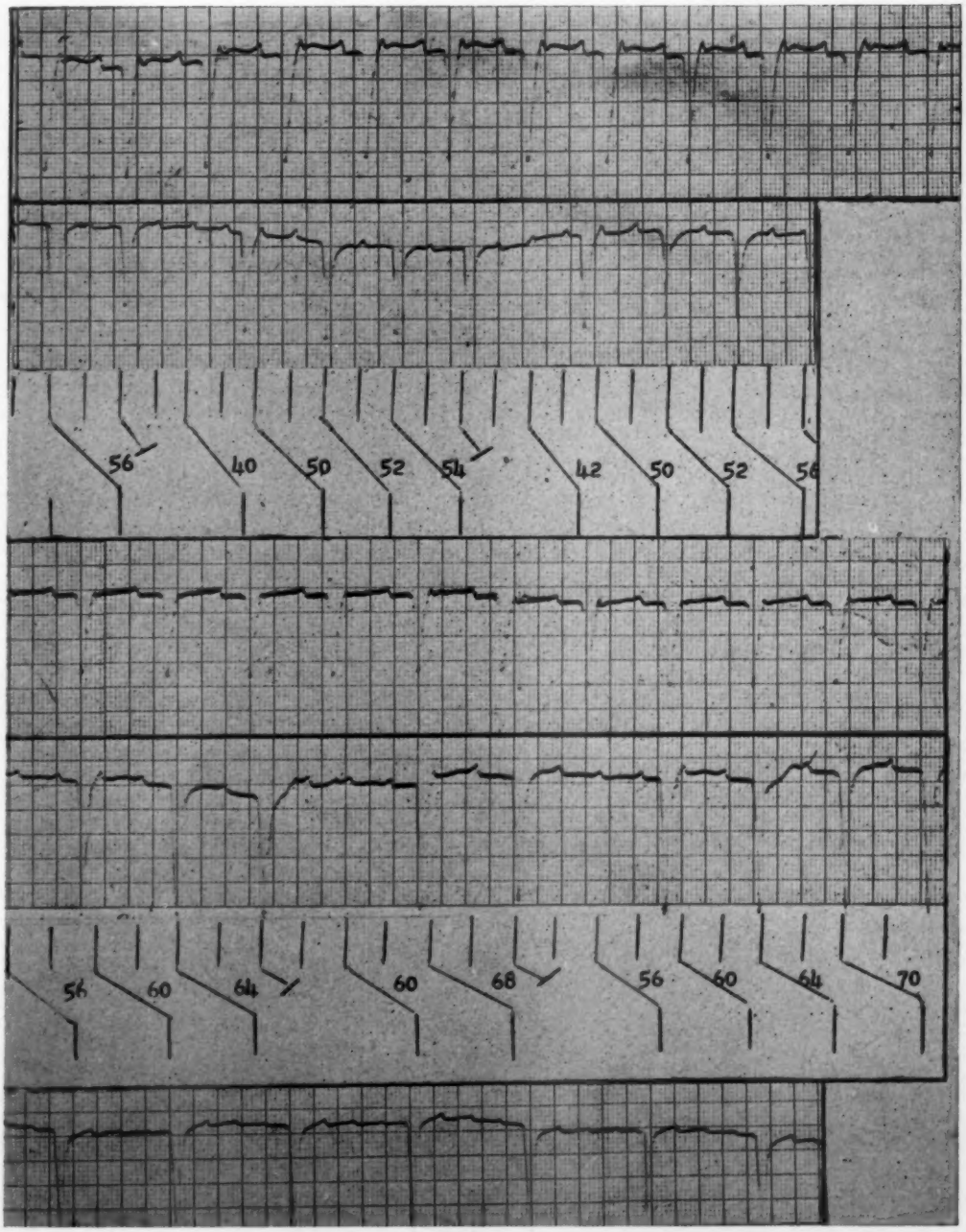

Fig. 6.—Electrocardiograms of Case 98, P.F., recorded at daily intervals, showing the stage of atrial flutter with 2:1 conduction (*A* and *C*), Wenckebach phenomenon (*B* and *D*), and 4:1 conduction (*E*). Note the occurrence of Wenckebach type of block (*D*) as the A-V conduction changed from 2:1 (*C*) to 4:1 (*E*). Conventions in the diagrams below *B* and *D* as in Fig. 5. Blood levels of quinidine: *A*, 4.05 mg. per liter; *B*, 4.00 mg. per liter; *C*, 4.10 mg. per liter; *D*, 2.30 mg. per liter; and *E*, 1.10 mg. per liter

Fig. 5.—Cont'd. *F*, Atrial flutter (f = 214) with 3:2 Wenckebach type of block as shown by the diagram below the tracing; blood level = 3.6 mg. per liter. *A* represents the atria, *A-V* the A-V junction, and *V* the ventricles. The vertical lines in the top and bottom rows represent the beginning of the atrial and ventricular complexes, respectively; the oblique lines, the conduction in the A-V junction from atria to ventricles; the short lines at right angles to the oblique lines, blockage of the impulses. The figures represent the F-R intervals in hundredths of a second. *G*, Atrial flutter (f = 214) with 4:1 block; blood level = 3.5 mg. per liter. *H*, Atrial flutter (f = 260) with 4:1 block; blood level = 2.0 mg. per liter. *I*, Atrial flutter (f = 290) with 4:1 block; blood level = 0.5 mg. per liter. *J*, Atrial fibrillation (f = 500); blood level, zero.

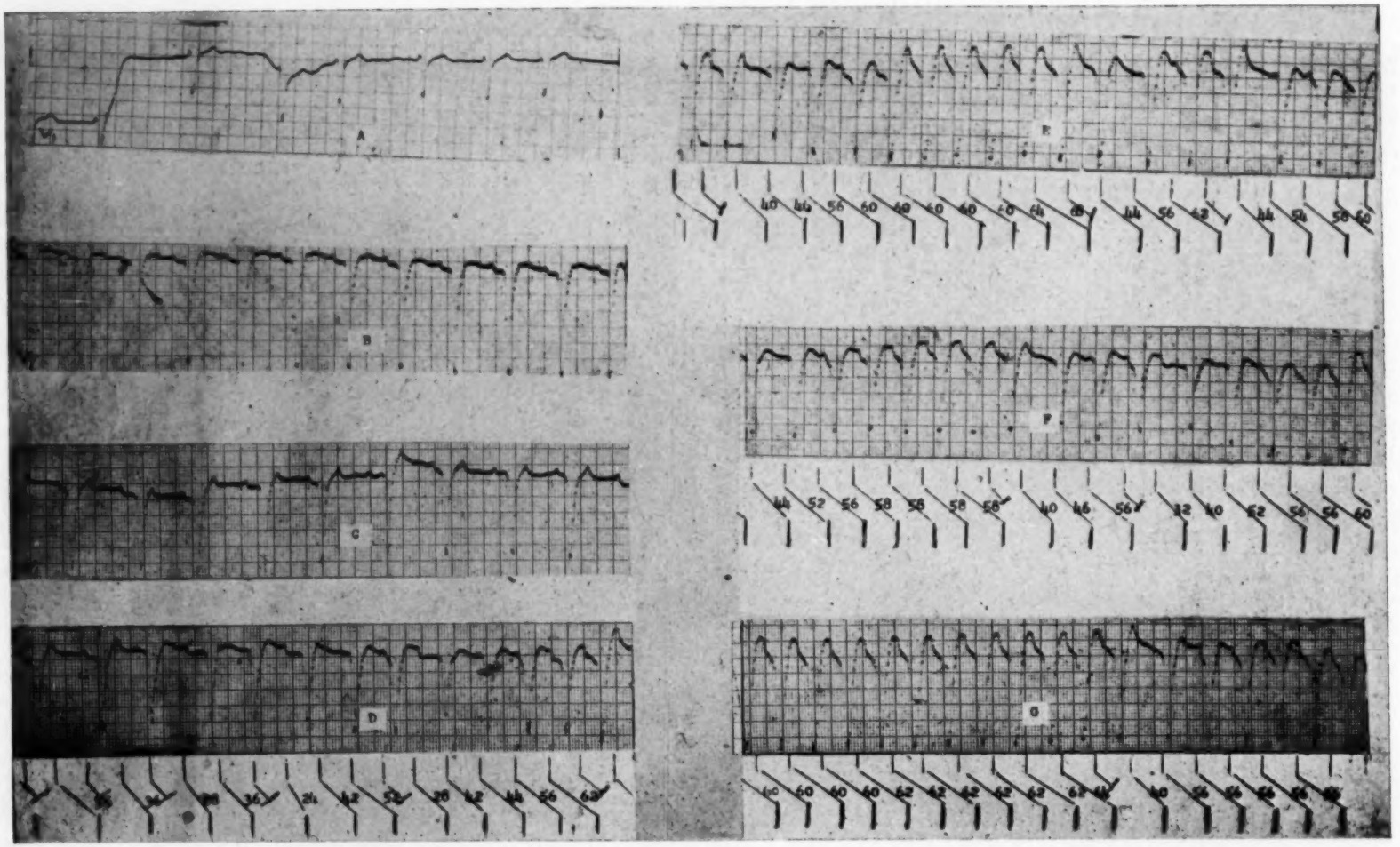

Fig. 7.—Electrocardiograms of Case 98, P.F., recorded during the second course of quinidine therapy, showing the development of 1:1 conduction in atrial flutter with Wenckebach periods. *A*, Control tracing showing atrial fibrillation. *B*, Second day of quinidine administration, showing atrial flutter (f = 188) with 2:1 block at a quinidine blood level of 3.93 mg. per liter. *C*, Third day of therapy, showing atrial tachycardia (a = 150) with 2:1 block at a blood level of 5.08 mg. per liter. *D-G*, Continuous tracing taken the evening of the same day as *C*, showing atrial tachycardia (a = 150) with 2:1 conduction at the start of *D* and then 1:1 conduction with Wenchebach phenomenon the rest of the tracing. Two hours later normal sinus rhythm returned. Conventions as in Fig. 5.

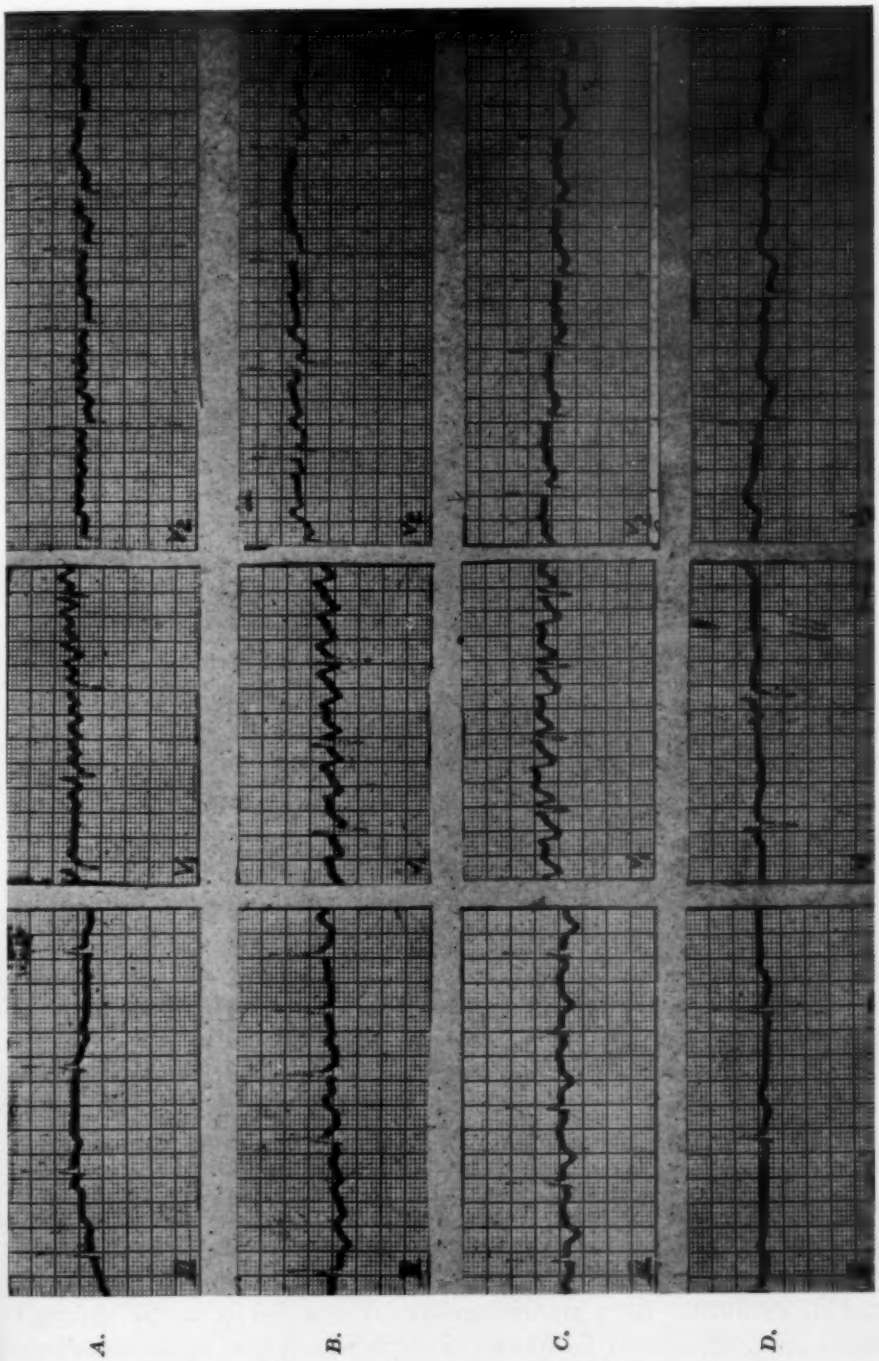

Fig. 8.—Electrocardiograms of Case 5, C.G., taken during the course of quinidine therapy, showing (1) the progressive slowing atrial rate with rising blood level of quinidine before eventual conversion to sinus rhythm, and (2) the difficulty in distinguishing between atrial flutter and tachycardia at a slow atrial rate. *A*, Control tracing showing atrial fibrillation. *B*, Atrial flutter (f = 188) at a blood quinidine level of 3.25 mg. per liter. *C*, Atrial tachycardia or flutter (188) at a blood level of 5.5 mg. per liter. Note the isoelectric T-P or P-P intervals in Leads III and V_2, although slight undulations could be detected in V_1. *D*, Sinus rhythm one day after *C* at a blood level of 2.03 mg. per liter.

ferentiating atrial tachycardia from flutter is the contour of the T-P or P-P intervals. In the tachycardia these intervals are briefly isoelectric, while in flutter most leads show continuous undulation of the base line.[11,18,19] However, in several cases studied by us, the atrial rate was around 150 to 188 per minute and the P-P intervals in Lead V_1 or V_2 was truly isoelectric, although slight undulations could be detected in Leads II and/or III during the same bout of the arrhythmia (Fig. 8). Prinzmetal[20] and Scherf[21] minimized the importance of isoelectric P-P or P-T intervals. Therefore none of the three criteria customarily recognized as necessary for differentiating atrial flutter from tachycardia, namely the atrial rate, the configuration of the P wave and P-P intervals, and the presence or absence of atrioventricular block, could be relied upon with certainty. Prinzmetal and associates[20] demonstrated the fundamental similarity in dogs of atrial flutter and atrial tachycardia, and suggested that the basic mechanism of atrial flutter and atrial tachycardia is a simple ectopic focus and is the same for both conditions. They proposed that the definition of "atrial tachycardia" might be altered to include all disturbances now diagnosed as flutter or tachycardia with supplementary description of the atrial rate with or without atrioventricular block.

Although the subject of atrial fibrillation and atrial flutter has been studied for many years, considerable controversy still exists concerning the mechanism of these arrhythmias and their interrelationship. Everyone accepted that the two conditions are only quantitatively different and that whatever mechanism may be responsible it forms the matrix for both. That a close relationship exists between the various atrial arrhythmias was first proposed by Sir Thomas Lewis, in 1912.[22,23] He wrote: "The conclusions that (1) simple premature auricular contractions, (2) small groups of the same, (3) paroxysms of tachycardia from single auricular foci, (4) auricular flutter, (5) paroxysms of tachycardia from two or more auricular foci, and (6) auricular fibrillation arise essentially in the same manner, namely, through the pathologic or heterogenetic origin of new impulses in the auricle, are clearly suggested by the facts at our disposal." Later Lewis[18] abandoned this view and attributed to atrial fibrillation and flutter a mechanism different from that common to atrial premature systoles and tachycardia. Over the years two main etiological concepts have been advanced for these atrial arrhythmias: (1) single heterotopic tachysystole, by which a single ectopic atrail focus of high inherent frequency will discharge repetitively, and thus act as atrial pacemaker[10,20,24-26]; (2) circus movement where one impluse traverses atrial tissue in a circular fashion with tangential offshoots (Lewis). Our study on the mode of action of quinidine on atrial fibrillation and flutter seemed to support the theory of unitary nature of all atrial arrhythmias. Quinidine converted atrial fibrillation to flutter, and atrial flutter to atrial tachycardia (usually with some degree of A-V block); intermediate forms were often obtained in between (Figs. 1, 3 to 5, 8 to 10). As reversion from sinus rhythm to atrial fibrillation took place, the gradual evolution from premature atrial systoles (Fig. 9) through atrial tachycardia (Fig. 10) and atrial flutter (Figs. 3 and 4) was again observed. That differentiation between atrial flutter and tachycardia may become difficult or almost impossible when the atrial rate is between 150 and 200 is well illustrated in several of our cases (Figs. 1, 5, 8, and 10).

Although the two theories, single heterotopic tachysystole and circus movement, seem mutually exclusive, perhaps without full justification, attempts

in reaching a compromise are not wanting in both past and present. Wenckebach and Winterberg[27] pointed out that once a point of re-entry has developed in excitable tissue, it can be considered as a focus firing rapid impulses in all

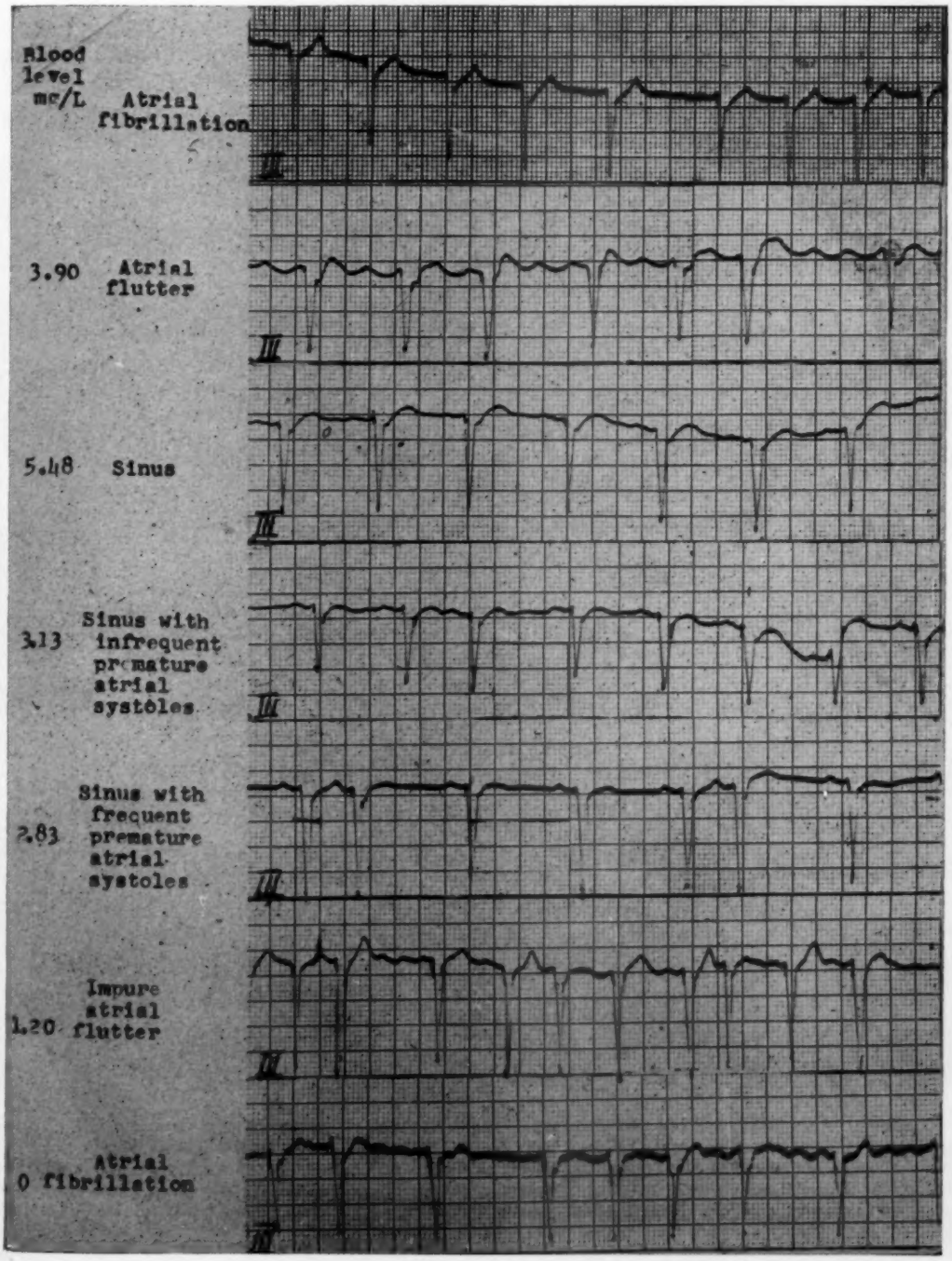

Fig. 9.—Electrocardiograms of Case 38, B.R., recorded at daily intervals, showing the progression of atrial fibrillation through flutter before conversion to normal sinus rhythm, and the reversion to atrial fibrillation through the stages of frequent atrial premature systoles and atrial flutter as the blood level of quinidine declined.

directions. Scherf,[12,28] as a result of his recent experiments, suggested that a rhythmic stimulus may be acting in atrial tachycardia and a continous stimulus in atrial flutter and fibrillation, that fibrillation cannot be due to a single mechanism, and that a circus movement is not the cause but a concomitant feature of rapid atrial activity.

The association of atrial flutter and tachycardia with Wenckebach periods has been reported sporadically in the literature.[16,18,29-35] Except in the article by Besoin-Santander, Pick, and Langendorf,[29] no report could be found in the

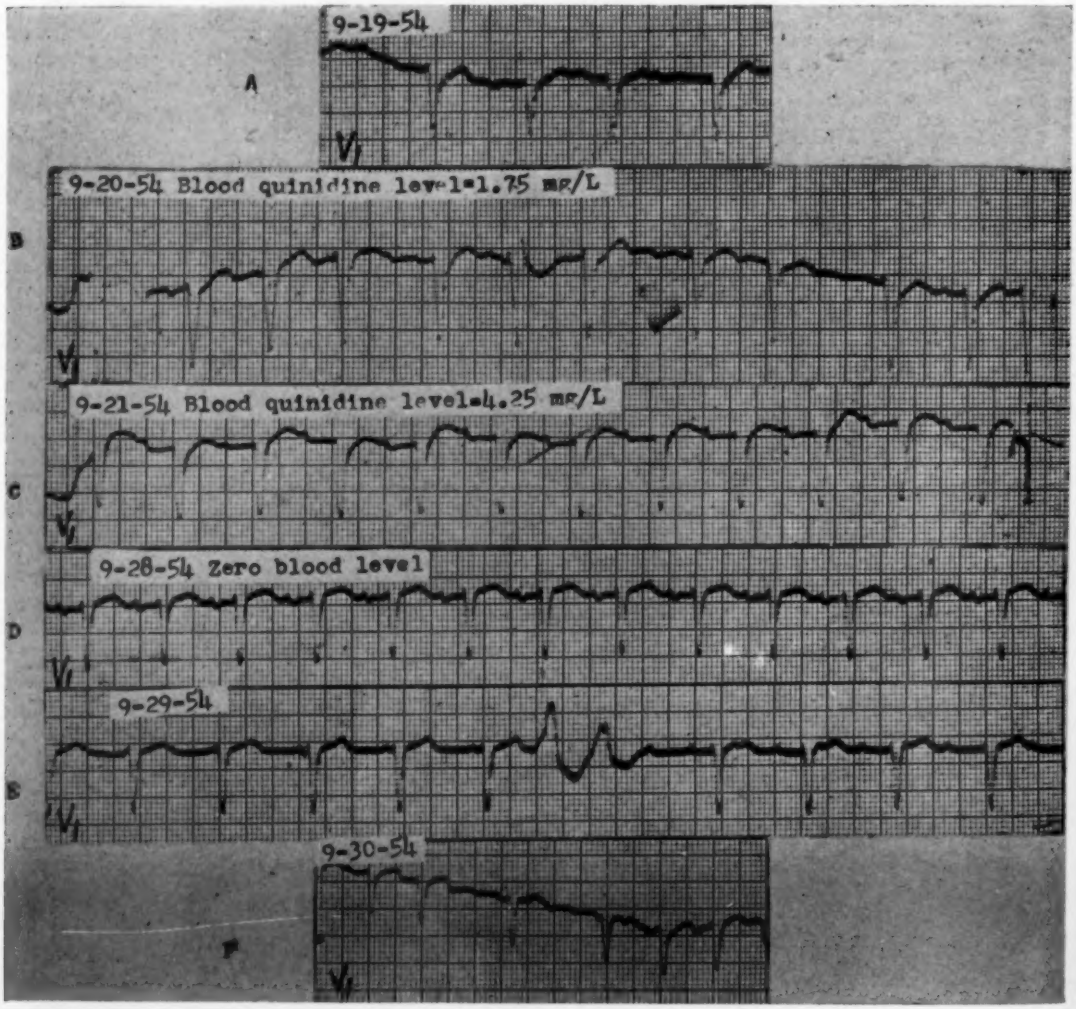

Fig. 10.—Electrocardiograms of Case 106, C. Mc., showing the sequence of events as atrial fibrillation was being converted to sinus rhythm during quinidine therapy and again as the arrhythmia recurred. Note the change of atrial fibrillation (*A*) to atrial flutter (*B*) before the restoration of sinus rhythm (*C* and *D*), and the transitory stage of atrial tachycardia with block (*E*) before the return of atrial fibrillation. Prolongation of the P-R interval was noted at the quinidine blood level of 4.25 mg. per liter (*C*).

literature which associated the occurrence of Wenckebach phenomenon during atrial flutter and atrial tachycardia with the use of quinidine. Inasmuch as it has not been previously reported during quinidine therapy for atrial fibrillation,

it is interesting to speculate as to the possible underlying factors which caused it to occur (fourteen times during 135 attempts at conversion in this study).

The influence of rapid atrial rate, of itself, upon the conduction tissue of the A-V node has been pointed out by Lewis and Master[36] and emphasized by Decherd and Ruskin[37] who observed dropped atrial beats occurring in response to rapid atrial action, and felt that the power of the A-V node to conduct decreased progressively during the period of rapid rate. In Figs. 5 and 6 where Wenckebach periods were noted, it is assumed that all flutter impulses penetrated some distance into the upper part of the A-V conduction system, and that only every second one was transmitted to the lower portion. Thus, a functional and constant A-V block higher in the node reduced by half the number of atrial impulses crossing the A-V junction, and another lower region of delayed conduction produced the progressive type of A-V block with eventual dropping of beats (i.e., Wenckebach phenomenon). Quinidine might facilitate the production of the Wenckebach phenomenon in two ways: (1) by depressing the conductivity of the A-V nodal tissue and (2) by vagal depression. The first effect is well illustrated in Cases 55 and 98 (Figs. 5 and 6); the induced atrial flutter had first a regular 2:1 conduction and later a 4:1 conduction with the Wenckebach type of block observed as an intermediary stage between the two. Quinidine then could depress the vagus nerve,[38-41] and vagal depression has been suspected as causing an incomplete A-V block with Wenckebach phenomenon.[42]

In the past there has been considerable difference of opinion as to the indications and contraindications for quinidine. One contraindication that has been held by some is the occurrence of atrial flutter during the course of quinidine therapy of atrial fibrillation. Lewis[43] stated that if atrial flutter develops during the treatment of atrial fibrillation with quinidine, the drug probably should be stopped because of the danger of developing a 2:1 or 1:1 flutter with disastrous clinical effects. Drury and Iliescu[44] also emphasized that, under the influence of quinidine, atrial fibrillation changes to sinus rhythm via a stage of flutter and advised against lowering the atrial rate below 200 because of the danger of 1:1 conduction with resultant rapid ventricular rate. White[45] states in his recent text "..If persistent atrial flutter appears it is best to stop the quinidine... Atrial flutter is a natural transitional stage in the change from atrial fibrillation to normal sinus rhythm, but it is usually brief and often too transient to be recorded electrocardiographically..."

In our own experience as well as in that of others[5-8] we have found that most patients passed through a stage of atrial flutter as atrial fibrillation underwent conversion to normal sinus rhythm during quinidine therapy, and that the appearance of atrial flutter in itself should not be a contraindication to further use of quinidine. In most instances if the dosage of quinidine is maintained or increased, conversion to a normal sinus rhythm will result. Digitalis should be used routinely, because of the possibility of the unexpected occurrence of 1:1 conduction. That digitalis will not always prevent this unfortunate type of accelerated conduction is clearly shown in the four instances in this study, in three of which 1:1 conduction occurred despite full digitalization. Six patients have been reported previously in whom atrial flutter with 1:1 conduction developed during quinidine therapy despite the concomitant use of digitalis.[5,46,47]

SUMMARY

1. Development of atrial flutter is a common result of quinidine therapy given for conversion of atrial fibrillation to normal sinus rhythm.

2. The fact that atrial fibrillation can be changed during quinidine therapy to atrial flutter or tachycardia before final conversion to sinus rhythm, and that when reversion takes place the rhythm again proceeds from sinus through atrial premature systoles, atrial tachycardia, and atrial flutter to atrial fibrillation lends support to the theory of unitary nature of the atrial arrhythmias.

SUMMARIO IN INTERLINGUA

Le disveloppamento de flutter atrial es un effecto commun del therapia a quinidina interprendite pro converter fibrillation atrial in normal rhythmos sinusal. Le apparition de flutter atrial per se non deberea esser interpretate como indication contra le continuation del therapia a quinidina. Si le dosage de quinidina es mantenite o augmentate, conversion al regular rhythmo sinusal occurre frequentemente. Durante le stadio del inducite flutter atrial, omne grados de conduction atrio-ventricular esseva trovate, includente le typo Wenckebach de bloco e le conduction 1:1. Iste ultime occurreva mesmo in le pressentia de digitalisation complete. Le factos que fibrillation atrial pote cambiar se sub therapia quinidinic in flutter atrial o tachycardia ante le advento final de conversion al regular rhythmo sinusal e que—quando reversion occurre—le rhythmo passa de novo via prematur systoles atrial, tachycardia atrial, e flutter atrial a fibrillation atrial, reinfortia le theoria del natura unitari del arrhythmias atrial.

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A CLINICAL EVALUATION OF ACETYL-DIGITOXIN

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THE advantages of the pure glycosides are well known. A new cardiac glycoside like acetyl-digitoxin therefore merits careful evaluation. Stoll and Kreis,[1] prepared acetyl-digitoxin from lanatoside A by enzymatic cleavage of one molecule of glucose. The resulting compound is digitoxin with an acetyl group attached to the alpha carbon of the side chain. Chemical analysis by Stoll and Kreis showed that acetyl-digitoxin is a well-defined pure glycoside which has no biologic assay variations. Rothlin[2] and Löffler and co-workers[3] have shown that acetyl-digitoxin is well absorbed, has excellent cardiotonic effects, and is less toxic than digitoxin. Löffler and associates placed acetyl-digitoxin midway between the glycosides digilanid and lanatoside C, and digitoxin in action.

In this clinical report on acetyl-digitoxin we have stressed the dosage required for minimum effective digitalization, maintenance dose and toxicity, since there is disagreement concerning these features of the drug.

METHOD OF STUDY

Rapid Digitalization.—The plan of study followed was that of DeGraff, Batterman, and Rose.[4] Patients in frank congestive heart failure were selected. They had the usual findings of right and/or left ventricular failure, tachycardia, with and without auricular fibrillation, basal râles, distended neck and antecubital veins, enlargement of the liver, ankle edema, orthopnea and dyspnea, prolonged circulation time, and decreased vital capacity.

The symptoms of congestive heart failure were evaluated initially by the authors and subsequent changes in symptoms were scrutinized by at least two of the authors before each dose of the glycoside was administered.

All patients of the rapid digitalization group were digitalized orally. They were selected because they had never received previous digitalis or mercurial diuretics. A program of hospitalization with bed rest, low salt diet of approximately 1.8 Gm. of sodium chloride, limitation of twenty-four-hour intake of fluid to 1,500 c.c. was instituted for one to three days without other forms of treatment.

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The control observations consisted of the following:

1. Venous pressure was measured directly with a water manometer. Circulation time was measured with Decholin. Vital capacity was determined by a McKesson-Scott respirometer.
2. Ventricular, pulse, and respiratory rates were taken every two hours during the first twenty-four hours and every four hours during the next two hospital days.
3. No digitalis and no mercurial diuretics were administered during the control period of from one to three days' observation. If the patient could not be maintained on this regimen, he was excluded from the series.
4. Daily weight was taken at the same time in the morning in pajamas and without shoes.
5. An electrocardiogram was made each day.
6. When toxicity occurred, notes were made regarding manifestation, time of day, date, and dosage used. Acetyl-digitoxin was immediately stopped and the duration of toxicity was observed.

Sixteen patients, varying in age from 57 to 78 years, were studied. Eleven patients had arteriosclerotic heart disease and five had, in addition, hypertensive heart disease. Five of these patients had auricular fibrillation with ventricular rates varying initially between 120 and 136 beats per minute. One patient had auricular flutter with an initial ventricular rate of 96 beats per minute. One patient had both arteriosclerotic and rheumatic heart disease. Four of the patients had the additional diagnosis of diabetes mellitus.

The Maintenance Study.—The maintenance group study was, for the most part, made in the Cardiac Clinic. The patients of this group were well compensated on their previous digitalis medication and did not require the use of mercurial diuretics. Acetyl-digitoxin 0.2 mg. was substituted for the previously satisfactory digitalis preparation, or glycoside, and taken at the same time each day. Twenty patients were treated who varied in age from 25 to 79 years. Their etiological diagnoses were arteriosclerotic heart disease in ten, rheumatic heart disease in seven, hypertensive heart disease in two, pulmonary heart disease (chronic cor pulmonale) in one. Additional diagnoses were diabetes in six, hypertension in four, chronic nephritis in two, and pulmonary disease in one. Six had auricular fibrillation with rates varying from 56 beats per minute to 75 beats per minute without pulse deficit.

At each clinic visit the following data were noted. Ventricular and pulse rates were taken for one minute after the patient had rested for fifteen minutes. Blood pressure, respiratory rate, and weight undressed and without shoes were noted. A control electrocardiogram and a repeat electrocardiogram were made every three weeks. The diet remained unchanged from the period of previous satisfactory control. Mercurial diuretics were not used unless absolutely necessary, and such patients were then removed from the study.

If decompensation or toxicity occurred, acetyl-digitoxin was discontinued and the patient was given his previously used digitalis preparation or glycoside. These patients were then removed from the study and a period of eight weeks was allowed to elapse before recommencing acetyl-digitoxin in order to allow for restoration of compensation and to allow for elimination of the drug. If, after eight weeks, neither decompensation nor toxicity occurred on a specific dose of acetyl-digitoxin, then the daily dose was increased to either 0.3 or 0.4 mg. until toxicity was reached. Later, in the study, when 0.1 mg. scored tablets became available, a small series of five patients were tried on this schedule.

The starting dose for the maintenance study was 0.2 mg. acetyl-digitoxin by mouth, but various dosage schedules were employed so that there was a total of thirty-nine trials.

TABLE I.

PATIENT	SEX	AGE	TOTAL DIGITALIZING DOSE	DIAGNOSIS	TOXIC DOSE	WEIGHT IN POUNDS	ARTERIAL PRESSURE (mm. Hg.)
L.B.	F	60	1.8	Auricular fibrillation	2.6	126 122	155/90 150/85
A.B.	M	73	1.4	Arteriosclerotic heart disease Congestive heart failure	3.4	145 140	125/80
L.L.	M	75	1.8	Diabetes Congestive heart failure	3.4	130 128	160/80 140/70
G.P.	F	65	1.8	Arteriosclerotic heart disease Hypertensive heart disease Auricular fibrillation Congestive heart failure	1.8	135 132	180/90 150/60
M.S.	F	62	1.6	Arteriosclerotic heart disease Auricular fibrillation	1.8		130/90 153/90
A.M.	M	64	1.8	Arteriosclerotic heart disease Hypertensive heart disease Congestive heart failure	2.0	148 132	180/110 165/110
I.E.	M	67	1.8	Arteriosclerotic heart disease Hypertensive heart disease Third degree heart block Congestive heart failure	2.6	144 136	260/90 240/90
S.G.	M	78	1.8	Arteriosclerotic heart disease Congestive heart failure Diabetes	3.0	150 142	150/75 145/70
M.M.	M	64	2.0	Arteriosclerotic heart disease Congestive heart failure Diabetes	3.4	158 154	120/85 120/80
D.S.	M	64	1.8	Diabetes Kimmelstiel-Wilson disease Hypertensive heart disease Congestive heart failure	2.8	150 148	170/90 160/80
J.L.	M	70	1.8	Auricular fibrillation Arteriosclerotic heart disease		126 126	125/70 125/70
M.A.	F	64	1.8	Arteriosclerotic heart disease with acute congestive heart failure			140/80 140/80
F.V.	F	67	1.8	Arteriosclerotic heart disease Congestive heart failure	2.4	110 110	126/72 120/80
J.R.	M	57	1.8	Rheumatic heart disease Arteriosclerotic heart disease Mitral insufficiency Aortic insufficiency	2.6	122 120	135/56 148/50
I.M.	M	70	1.8	Auricular flutter Arteriosclerotic heart disease	2.6	120 120	
M.P.	F	64	2.0	Auricular fibrillation Arteriosclerotic heart disease	2.6	118 118	

SUMMARY OF DATA

APICAL RATE PER MINUTE	RADIAL PULSE RATE PER MINUTE	RESPIRATORY RATE PER MINUTE	PULMONARY EDEMA	ENLARGEMENT OF THE LIVER	PERIPHERAL EDEMA	VENOUS PRESSURE	CIRCULATION TIME (VEIN-TO-TONGUE)	VITAL CAPACITY %
136 84	110 84	20 20	+− +−	0 0	0 0	190 150		59 70
96 64	96 64	36 20	++ 0	0 0	++ 0	160 140		60 70
90 76	90 76	20 18	++ 0	0 0	0 0	110		72 80
70 56	54 56	20 18	++ 0	2 FB 0	0 0	196 140		63 75
120 72	100 60	24 20	++ 0	2 FB 1 FB	++ 0	110 90		40 60
100 72	100 72	30 20	++ 0	3 FB 2 FB	+++ 0	170 124		25 60
40 38	40 38	24 20	0 0	3 FB 1 FB	++ 0	150 120		71
95 72	95 72	24 16	++ 0	4 FB 2 FB	++ 0	135 105		45 67
90 70	90 70	24 20	++ 0	0 0	++ 0	200 95		35 93
80 74	80 74	20 18	0 0	0 0	0 0	150 100	45 18	
130 80	96 80	24 18	0 0	0 0	0 0			
100 80	100 80	28 16	+++ 0	2 FB 0	0 0			
82 72	82 72	24 18	++ 0	4 FB 0	++ 0	200 100	38 18	
98 80	98 80	26 18	++ 0	2 FB 1 FB	+ 0	200 100	18 12	
96 78	96 78	22 18	0 0	0 0	0 0			
120 80	110 80	20 18	0 0	0 0	0 0			

RESULTS

Rapid Digitalization. The range of the digitalizing dose was between 1.4 and 2.0 mg. Twelve of the sixteen patients were digitalized in twenty-four hours at a dose of 1.8 mg. The remaining four patients were digitalized in twelve hours at 1.4 mg., eighteen hours at 1.6 mg., and in thirty hours at 2.0 mg.* Table I summarizes the data of this group.

The range of the toxic dose was between 1.8 and 3.4 mg. with an average of 2.6 mg. The therapeutic ratio was obtained by dividing the therapeutic dose by the toxic dose, and was found to be 0.69. Table II summarizes the data on the toxicity of acetyl-digitoxin in this group.

TABLE II. SUMMARY OF TOXIC SYMPTOMS IN THE FOURTEEN PATIENTS CARRIED TO TOXICITY ON RAPID ORAL DIGITALIZATION

SYMPTOM	NUMBER OF PATIENTS	TOXIC DOSE IN MG.		DURATION IN HOURS	
		RANGE	AVERAGE	RANGE	AVERAGE
Anorexia and nausea	8	1.8–3.4	3.7	36–48	43
Nausea with vomiting	4	2.4–2.8	2.6	12–72	42
Premature ventricular beats	1	2.0	2.0	24	24
Rash	1	3.0	3.0	60	60
Total	14	1.8–3.4	2.64	12–72	42.5

The Maintenance Study.—The twenty patients of this group served for thirty-nine trials on various different dosage schedules. The success of the maintenance dose and of the production of toxicity on a given schedule is shown in Table III.

TABLE III. RESULTS OF THIRTY-NINE TRIALS IN TWENTY PATIENTS ON VARIOUS DOSES OF ACETYL-DIGITOXIN

	DAILY DOSE IN MG.				
	0.1	0.15	0.2	0.3	0.4
Number of trials	5	4	20	2	8
Well maintained without toxicity	1	4	7		
Well maintained with slight toxicity			2		
Toxicity. The drug was discontinued			6	2	7
Increased degree of congestive heart failure without toxicity	4				
Increased degree of congestive heart failure with toxicity			5		1

The average maintenance dose is in the range of 0.15 mg.
Eleven out of twenty patients showed toxicity at 0.2 mg.
Seven out of twenty were well maintained on 0.2 mg.
Four out of five patients showed increasing congestive failure on 0.1 mg. daily.

*Since the initial dose was 1.0 mg., each additional 0.2 mg. represents six hours of elapsed time.

It can be seen that 0.2 mg. does not represent a good "average" maintenance dose since twelve of the twenty patients became toxic at this dose. A schedule of 0.1 mg., on the other hand, did not represent a satisfactory maintenance since four out of five patients on this schedule decompensated. A summary of the toxic manifestations of the maintenance group is shown in Table IV.

The therapeutic effects observed in both groups were those usually found after the use of any digitalis preparation, namely a decrease in tachypnea, pulmonary edema, hepatomegaly, peripheral edema, venous pressure, circulation time, and an increase in vital capacity.

TABLE IV. A SUMMARY OF THE TOXIC MANIFESTATIONS ON THE MAINTENANCE SERIES

SYMPTOM	NUMBER OF PATIENTS	DOSE IN MG.	WEEKS ON MEDICATION		DURATION IN HOURS	
			RANGE	AVERAGE	RANGE	AVERAGE
Nausea	4	0.2	1–4	2.5	36–48	42.5
Vomiting	2	0.2	2–4	3	48–60	54
Rash	2	0.2	2	2	72–96	84
Confusion	3	0.2	1–4	2	36–240	108
Bigeminy	1	0.2	3	3	1 week	1 week
2 degree heart block	1	0.2	3	3	72	72
Anorexia	2	0.3	2–6	4	36–48	42
			DAYS ON MEDICATION			
Vomiting	5	0.4	2–14	4	48–60	50
Anorexia	2	0.4	3.6	4	48–72	60
Visual	1	0.4	14	14	60	60

The toxic manifestations were similar to those observed in other digitalis preparations. The earliest symptom of toxicity with acetyl-digitoxin was anorexia. Most of the toxic manifestations were referable to the gastrointestinal tract rather than to the heart. In thirty-seven trials in which toxicity was reached (all but two of the thirty-nine trials), and the drug discontinued, gastrointestinal symptoms predominated in twenty-nine trials and cardiac arrhythmias in only three. Table II lists the toxic manifestations of the rapid digitalization group and Table IV the toxic manifestations of the maintenance group.*

*Other signs appeared that indicated an individual incompatibility to the drug rather than actual toxicity to digitalization. These were cutaneous rash and mental confusion (Table IV). In both series three patients developed a maculopapular nonpruritic rash, which disappeared in fourteen days in one while still on the drug. In a second, the rash disappeared three days after cessation of the drug, only to reappear again five days after the drug was resumed. In the third, the rash disappeared sixty hours after the drug was stopped. Three of the patients on the maintenance series developed acute brain syndromes with disorientation and confusion as to time, place, and person. This cleared in from two to ten days following withdrawal of the drug. One of the three resumed acetyl-digitoxin later without ill effect. In one, any implication of the drug as the cause of the mental changes must be held in abeyance, since within two days of developing the mental confusion this elderly patient expired from a proved cerebrovascular accident. It should be noted that the two patients who developed cardiac arrythmias, bigeminy in one and second degree heart block in the other, also showed rhythmic aberrations on other digitalis drugs at equivalent doses which are well tolerated by the majority of patients. In this respect these patients also tolerated acetyl-digitoxin very well.

TABLE V. RESULTS OF VARIOUS AUTHORS ON MAINTENANCE AND DIGITALIZING DOSES, AND THEIR DIFFERENT SCHEDULES

	DIGITALIZING DOSE (DAYS)								MAINTENANCE DOSE			TOXIC DOSE		THERAPEUTIC RATIO
	PATIENTS	RANGE	1	2	3	4	5	6	PATIENTS	RANGE	AVERAGE	RANGE	AVERAGE	
Gunther et al.	16	1.4–2.0	1.8	2.8					20	0.5 –0.20	closer to 0.15	1.8–3.4	2.6	69
Heinrich and Delius	13	1.5–4.6*				2.2			44	0.05–0.5	0.20			
Augsberger							3.2†				0.25			
Löffler et al.	60	2.0–6.0‡	2.4§		3.4	4.0			120	0.1 –0.6		4.8–7.5	5.6	65
Hausler and Hortnagl	Mild failure						2.0–2.5‖		42	0.08–0.16				
	Severe failure							4.5¶		0.25–0.33				
Thorner and		2.2–3.2	2.2#	3.2***										
Goldfarb	82		2.4**						82	0.1 –0.2	0.15			
Maher and Pullen	29	1.5–3.0	1.8							0.1 –0.15				

*Compensated after a total dose of 1.5 to 4.6 mg. given in 3 to 6 days with an average of 2.2 mg. in 4.4 days.
†1.2 mg. first day, 0.7 mg. second day, 0.5 mg. third day, 0.4 mg. fourth and fifth days.
‡Some patients were digitalized in one day, most were given 0.4 mg. bid or tid.
§Given either as a single dose or 2 to 3 smaller doses.
‖0.5 mg. per day for 4 to 5 days.
¶0.75 mg. per day for 5 to 6 days.
#One dose compensated in 8 hours.
**0.8 mg. q4h-compensated in 12 hours.
***0.4 mg. q6h-compensated in 48 hours.

DISCUSSION

There is a variation in doses of acetyl-digitoxin for both rapid and maintenance digitalization by different observers when given orally. This is shown in Table V. It is to be noted that European workers and Thorner and Goldfarb[5] employed larger doses for both digitalizing and maintenance doses (but especially the initial digitalizing doses) than we found necessary. Thus Löffler and associates[3] used 2.0 to 6.0 mg. for the digitalizing dose and 0.1 to 0.6 mg. for maintenance dose, whereas we have employed 1.4 to 2.0 mg. for digitalizing, and 0.1 to 0.2 mg. for maintenance.*

TABLE VI. COMPARISON OF THE THERAPEUTIC DIGITALIZING DOSE AND THE TOXIC DOSE OF VARIOUS DIGITALIS DRUGS

DRUG	NUMBER OF PATIENTS	THERAPEUTIC DOSE		TOXIC DOSE		THERAPEUTIC RATIO*
		RANGE	AVERAGE	RANGE	AVERAGE	
Gitalin	24	3.0–10.5 mg.	5.6 mg.	5.25–25.5 mg.	15 mg.	36.9
Digitalis leaf	36	0.9– 2.7 Gm.	1.5 Gm.	1.2 – 3.6 Gm.	2.24 Gm.	66.5
Digitoxin	27	0.9– 4.8 mg.	2.4 mg.	1.5 – 9.3 mg.	4.1 mg.	58.0
Digoxin	22	2.0– 6.0 mg.	3.77 mg.	3.0 –12.0 mg.	6.2 mg.	60.6
Acetyl-digitoxin	16	1.4– 2.0 mg.	1.8 mg.	1.6 – 3.4 mg.	2.6 mg.	69.2

Data for gitalin, digitalis leaf, digitoxin, and Digoxin reprinted with kind permission of Dr. Batterman, Circulation 5:201, 1952.

***Therapeutic Ratio equals Therapeutic dose per Toxic dose × 100.**

It is difficult, for example, to accept the European report that 0.3 mg. is a suitable daily maintenance dose when 65 per cent of our patients became toxic on 0.2 mg. daily. The studies of Maher and Pullen[6] were more in accord with our experience, for they showed that oral digitalization could be achieved with 1.8 mg. given in twenty-four hours or by doses of 1.5 to 3.0 mg. in three to six days. The maintenance dose of Maher and Pullen was 0.1 to 0.15 mg. daily.

The reasons for these differences deserve comment and understanding, otherwise uniformity of dosage for acetyl-digitoxin will not be achieved. We have followed the method of study elaborated by DeGraff and co-workers[4] which utilizes a relatively small initial dose followed by fixed increases and most careful observations of the patient until the overall manifestations of congestive heart failure are relieved. For example, in patients with auricular fibrillation and rapid ventricular rates, we did not slow the pulse to an arbitrary rate of 70 to 75 beats per minute as followed by Löffler and associates.[3] By contrast, the European workers, notably Löffler and associates, used Gold's method[7] of relatively large initial doses for digitalization and continued administering acetyl-digitoxin until an arbitrary slowing of the pulse to 70 to 75 beats per minute was achieved. As can be seen in Table I, we achieved good clinical effect with pulse rates reduced to 80 beats per minute. Thus it is our opinion that these workers used a larger dose of acetyl-digitoxin to achieve their therapeutic effect than was probably needed.

***0.15 mg. probably represents the average daily maintenance dose.**

We feel that the establishment of the *minimum optimum therapeutic dose* is the goal in evaluating a digitalis glycoside. DeGraff and co-workers have pointed out that "considerable more of a digitalis preparation can be given *beyond the optimum dose* with the same therapeutic effect." This is illustrated by comparison of the percentage of patients who exhibited good, fair, and poor responses to acetyl-digitoxin, in Löffler's and our series.

	Löffler et. al	*Gunther et al.*
Number of patients	120	20
Good or excellent	43%	50%
Fair	38%	25%
Failure	19%	25%

The possibility of redigitalization which might occur in patients who have discontinued the drug for a few weeks was avoided by studying only those patients in our rapid oral digitalization group who had never received digitalis before and were not so sick that intravenous digitalization was required.

It is worth stressing that toxic manifestations encountered with acetyl-digitoxin were gastrointestinal rather than cardiac. This may be one reason why toxicity was detected quite early in our study; another reason being the extreme care exercised by us in questioning the patient prior to giving additional doses of the medication. The difference between appearance of anorexia and nausea may be one or two tablets and this would alter the optimum minimal therapeutic dose considerably. Rothlin and Bircher[8] have pointed out that acetyl-digitoxin is derived from a highly purified substance containing 95 per cent active digitoxin, and never less than 90 per cent, whereas other digitoxin preparations may have as low as 80 per cent active ingredients. The purity of acetyl-digitoxin may be an important factor in the narrow range of digitalizing dosage we encountered.

CONCLUSIONS

1. The range for digitalization by mouth was 1.4 to 2.0 mg. in a period of twelve hours for the smaller dose and thirty hours for the large dose.
2. Seventy-five per cent of patients were digitalized with a dose of 1.8 mg. in a twenty-four hour period.
3. The average maintenance dose appears to be 0.15 mg. daily.
4. The toxic dose in rapid oral digitalization ranged between 1.8 and 3.4 mg. with an average of 2.6 mg. in a forty-eight-hour period.
5. The therapeutic ratio is 0.69, which compares favorably with other digitalis glycosides.
6. Toxicity is manifested first by gastrointestinal symptoms, namely anorexia, which is later followed by nausea and vomiting. These symptoms lasted on an average of forty-three hours after the drug was discontinued.
7. Cardiac arrhythmias occurred in the minority of patients.
8. The oral digitalizing dose of acetyl-digitoxin has a narrow range, 75 per cent of the patients being digitalized in twenty-four hours with 1.8 mg.

SUMMARIO IN INTERLINGUA

Le nove, chimicamente pur glycosido, Acylanido (acetyl-digitoxina), un preparato ab *Digitalis lanata*, esseva studiate relative a su minimal dose efficace pro rapide digitalisation oral, su dose de mantenentia, e su toxicitate. Pro rapide digitalisation il esseva constatate que 1,8 mg per 24 horas, administrate in doses dividite, es le minimal dose efficace in le caso de patientes qui non habeva previemente essite digitalisate o qui habeva essite tractate con preparatos mercurial. Le dose de mantenentia variava inter 0,1 e 0,3 mg.

Nostre observationes indica que Acylanido ha le avantages de un rapide declaration de activitate, un alte velocitate de dissipation, e le manifestation de anorexia como symptoma initial de toxicitate. Nausea e vomito se manifesta ante que irregularitates cardiac deveni observabile. Le activitate pharmacologic de iste glycosido es apparentemente inter illos de Lanatosido C e de Digitoxina. Illo es un substantia de alte grado de purification, e su effecto therapeutic es predicibile intra stricte limites minimo-maximal de digitalisation.

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GITALIN THERAPY OF CONGESTIVE HEART FAILURE IN THE AGED

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AT ALL ages digitalis glycosides are useful in the treatment of congestive heart failure to improve the function of the impaired myocardium, to enhance the force of systolic contraction of the diseased and dilated heart, and to slow the heart rate in auricular fibrillation and other supraventricular arrhythmias. The primary aim of digitalis therapy is to obtain the desired therapeutic effect without the occurrence of toxicity. This objective is often difficult to achieve in elderly patients with heart disease whose myocardial reserve may be greatly diminished, or who may be relatively refractory to usual doses of digitalis and in whom the therapeutic range of a digitalis preparation may be consequently narrowed. For these and other reasons, treatment of congestive heart failure in elderly patients presents problems of greater magnitude than in younger persons.[1]

Although cardiac glycosides in general have similar therapeutic ranges, we became interested several years ago in gitalin. Clinical reports[2,3] indicated that this water-soluble, amorphous mixture of glycosides extractable from *Digitalis purpurea* possesses an unusually wide therapeutic range. We, therefore, selected gitalin for therapeutic evaluation in a series of elderly patients with congestive heart failure from a variety of causes. Because of their age, chronic cardiac condition, and especially poor myocardial reserve, our patients presented a rigid test for this preparation.

PRESENT STUDY

Our study concerned the clinical management of seventy-seven unselected elderly patients with congestive heart failure who were admitted to the Ann Lee Home over a three-year period. The longest duration of treatment was 48 months, the shortest 2 weeks, and the average, 12.7 months. The group was composed of forty-four men and thirty-three women with ages ranging from 58 to 93 years, and averaging 78.4 years (Table I).

On admission, all patients were in moderate or severe congestive failure and the majority were seriously ill. Sixty persons had not received digitalis prior to admission; seventeen had been treated unsuccessfully with other digitalis preparations.

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TABLE I. AGE AND SEX DISTRIBUTION OF SEVENTY-SEVEN PATIENTS WITH CONGESTIVE HEART FAILURE

AGE	MALE	FEMALE	TOTAL
51–60	2	1	3
61–70	17	7	24
71–80	16	10	26
81–90	8	13	21
91 plus	1	2	3
Total	44	33	77

Diagnostic Procedures.—Congestive heart failure was diagnosed on the basis of a medical history and the usual symptoms and signs elicited on physical examination. Routine chest roentgenograms and serial 12-lead electrocardiograms were taken throughout the study to check the progress of treatment. Routine complete blood counts, urinalyses, serological tests, blood chemistry measurements, and occasional ballistocardiograms were also obtained.

Treatment of Previously Undigitalized Patients.—On admission, sixty undigitalized individuals with heart failure were temporarily placed at bed rest and digitalized. Seven in this group who were critically ill were digitalized orally as rapidly as possible with 3 mg. of gitalin* initially, and 3 mg. every two hours for at least two additional doses. After twelve to forty-eight hours these patients were maintained on daily oral doses of 0.5 to 1.5 mg.

The remaining fifty-three patients received no medication until they had obtained maximum benefit from bed rest. They were then digitalized with orally administered gitalin by the rapid or slow methods suggested by Batterman and associates.[2] Thirty-seven patients were digitalized in six to nine days; sixteen patients were digitalized in thirty-six to forty-eight hours. After they had improved, activity commensurate with their cardiac function was permitted.

A nutritious, balanced institutional diet was served to all patients. It was not found practical to restrict closely the dietary intake of sodium or to diverge widely from the standard routine of general nursing care ordinarily provided by the regular hospital staff. Adjunctive therapy was kept minimal. Parenteral diuretics, opiate sedatives, oxygen, and other measures were ordered only when necessary to ensure the well-being of the patients.

GITALINIZATION

The initial gitalinizing doses administered to fifty-three patients ranged from 2.5 to 22.5 mg., and averaged 7.0 mg. Approximately 155 trials were required to arrive at these individual doses (Table II).

Five patients manifested early signs of toxicity, such as nausea or ventricular premature contractions, during this phase of treatment. Three of these five patients subsequently tolerated reduced doses of gitalin. The remaining two patients could not tolerate the drug at all in doses sufficient to control their heart failure.

*Supplied as Gitaligin by White Laboratories, Inc., Kenilworth, N. J.

TABLE II. TRIALS OF DOSAGE IN THE GITALINIZATION OF FIFTY-THREE PATIENTS WITH CONGESTIVE HEART FAILURE

DOSE OF GITALIN IN MG.	NUMBER OF PATIENTS	NUMBER OF TRIALS
5.0 or less	3	8
5.5– 6.0	12	31
6.5– 7.0	16	39
7.5– 8.0	8	27
8.5– 9.0	5	21
9.5–10.0	2	8
10.5–11.0	1	3
11.5–12.0	2	8
12.5–13.0	1	2
13.5–14.0	1	3
14.5–15.0	0	0
15.5 or more	2	5
Total	53	155

Maintenance Therapy.—Safe and effective maintenance therapy with digitalis glycosides had been a problem at our institution until we used gitalin. Although previous investigators recommended approximately 0.5 mg. of gitalin as an average maintenance dose, we found this dose less than effective for most of our patients. We then began maintenance therapy routinely with 1.0 mg. daily, relying upon the previously reported greater therapeutic range of gitalin as our safety factor. Fifty-three patients received from 0.5 to 2.5 mg. (averaging 0.92 mg.) as a daily maintenance dose. Only two of the fifty-three patients could not be maintained effectively and safely within this dosage range.

Gitalin Treatment of Patients Refractory to Other Cardiac Glycosides.—When admitted to the Ann Lee Home, seventeen patients were receiving ordinarily adequate doses of other digitalis preparations, chiefly digitoxin, but were found to be in states of uncontrolled congestive failure or digitalis toxicity. After being put to bed on admission and clinically evaluated, these patients were subsequently switched to comparative dosage levels of gitalin (Table III).

TABLE III. COMPARATIVE DOSAGE TABLE

DIGITALIS PREPARATION	AVERAGE DAILY MAINTENANCE DOSE
Gitalin	0.5 mg.
Digitalis leaf	0.1 Gm.
Digitoxin	0.1 mg.
Digoxin	0.5 mg.

Trials, similar to those described by Batterman,[2] were used to determine optimal response to a given daily maintenance dose of the drug. Forty-five trials were run, using daily doses ranging from 1.0 mg. to 2.5 mg.

In this manner fifteen of the seventeen patients were controlled by gitalin without toxicity. Two could not be controlled without toxicity at any dosage level (Table IV).

TABLE IV. MAINTENANCE THERAPY WITH GITALIN IN SEVENTEEN PATIENTS REFRACTORY TO OTHER DIGITALIS PREPARATIONS

DOSE OF GITALIN (MG.)	NUMBER OF TRIALS		NUMBER OF PATIENTS	
	WELL MAINTAINED	DEVELOPED TOXICITY	WELL MAINTAINED	DEVELOPED TOXICITY
0.5	8	0	1	0
1.0	16	1	7	0
1.5	7	1	5	1
2.0	5	6	1	1
2.5	1	0	1	0
Total	37	8	15	2

TYPICAL CASE RECORDS

The following three cases illustrate some problems encountered in this group of elderly patients with congestive heart failure and demonstrate how they were treated successfully, principally with gitalin and rest.

CASE 1.—J. A., a 72-year-old farmer, entered the Ann Lee Home in early December, 1951, complaining of severe shortness of breath. Blood pressure was 200/100 mm. Hg. The heart was enlarged to the left. Auricular fibrillation was present. Scattered râles were heard over both bases. On Dec. 20, 1951, his temperature was 101.6° F. His electrocardiogram showed rapid auricular fibrillation with an average ventricular rate of 150 beats per minute. On this day he received 3 mg. of gitalin at 1 and 4 P.M. The next day his heart rate was 85 beats per minute. He was then maintained successfully on 1 mg. of gitalin daily.

On Jan. 17, 1952, gitalin was discontinued to ascertain if the patient would remain compensated. By Feb. 14, 1952, the patient was in moderate heart failure and again required gitalinization. On March 21, 1952, 30 grains of quinidine reverted the auricular fibrillation to sinus rhythm. He remained fully compensated until he died June 20, 1952, at St. Peter's Hospital from a carcinoma of the head of the pancreas.

Résumé.—This is an interesting case of a patient with congestive heart failure and auricular fibrillation who was successfully digitalized on 6 mg. of gitalin and then successfully maintained on 1 mg. daily until his death from carcinoma of the pancreas.

CASE 2.—J. O., 72 years old and weighing 225 pounds, was maintained on gitalin from Dec. 16, 1952, until Feb. 23, 1953, when it was discontinued to ascertain if his heart failure would return. Although the roentgenogram of April 22, 1953, revealed marked heart enlargement and pulmonary engorgement, the patient remained symptom-free until Jan. 11, 1954, when he complained of marked shortness of breath. On this day his electrocardiogram showed auricular fibrillation with an average ventricular heart rate of 120 beats per minute. He received 3 mg. of gitalin at 1:30 and 2:30 P.M. Twenty hours later his ventricular rate was 75. Subsequently he was maintained on a daily dose of 1.5 mg. of gitalin for a short time and then on 0.5 mg. His electrocardiogram on June 22, 1954, showed auricular fibrillation with an average heart rate of 60 beats per minute. X-ray on this day showed improvement in heart size and pulmonary congestion. He has since remained well for over one year.

CASE 3.—B. H. D., a 64-year-old farm worker, entered Ann Lee Home in 1951 with arteriosclerotic cardiovascular disease. Examination on Aug. 2, 1951, revealed an elderly, completely deaf, dyspneic man with distended neck veins. Blood pressure was 130/80. The heart was markedly enlarged to the left anterior axillary line. Heart rhythm was irregular with an apical heart rate of 150 beats per minute. Coarse râles were heard at both bases. The abdomen was

distended; the liver markedly enlarged. The scrotum was edematous. One-plus pitting edema of both legs was present. The electrocardiogram showed rapid auricular fibrillation and left heart strain. Average ventricular rate was 150. Chest x-ray revealed a markedly distended heart, fluid at both bases, and moderate pulmonary congestion.

Initial treatment on Aug. 3, 1951, consisted of 1.2 mg. of digitoxin orally, followed by 0.2 mg. daily and Mercuhydrin. Since the heart failure was apparently uncontrolled on August 14, digitoxin was increased to 0.4 mg. daily for three days and then reduced to 0.2 mg. daily. The patient improved but slightly. The heart remained enlarged. On August 21, the heart rate was 92 and the patient still in heart failure. For two days 0.4 mg. of digitoxin was again given and then reduced to 0.2 mg. daily. On August 28, dyspnea and peripheral edema still made him uncomfortable and his heart rate remained elevated. On October 1, digitoxin was substituted by 0.5 mg. gitalin. On October 18 this dose was increased to 1 mg. daily. For the next four years his average daily maintenance dose remained 1 mg. With gitalin he maintained good cardiac compensation, showed a marked decrease in heart size roentgenologically, and returned to light work.

Résumé.—This interesting case illustrates how a patient was successfully maintained for four years on gitalin without toxic effects after responding relatively poorly to digitoxin.

DISCUSSION

In the successful management of congestive heart failure the causes which Sonnek[4] has classified as (1) underlying, and (2) precipitating must be considered at all ages. Successful therapy depends upon the underlying as well as the precipitating factors, which in turn may be intrinsic or extrinsic. In our study one or more underlying causes of cardiac decompensation were frequently evident in the same patient. Table V lists the underlying factors of the heart disease in our group of elderly patients. As may be expected, arteriosclerosis was the most common underlying factor (58.2 per cent). Hypertension, presbycardia, and rheumatic heart diseases were the next commonest factors. Other underlying causes included syphilis, chronic cor pulmonale, and endocrine disorders. Among the precipitating causes paroxysmal arrhythmias, anemias, tumors, bronchopulmonary and other infections, injuries, environmental stress (including continual overwork), and pulmonary embolism occurred almost in this order. Our own post-mortem studies show that repeated pulmonary emboli can be a precipitating cause of intractable congestive heart failure in the aged.

TABLE V. CAUSES OF HEART DISEASE IN GROUP

ETIOLOGY	INCIDENCE (%)
Arteriosclerosis	58.2
Arteriosclerosis and hypertension	26.6
Hypertension	5.1
Presbycardia	3.8
Rheumatic	2.3
Others	4.0

Proper digitalization, essential at all ages, is especially important in elderly patients whose lives may depend upon prompt successful digitalization. The longer the elderly patient remains decompensated, the more his meager cardiac reserve is dissipated and his physical and mental resiliency deteriorates. The

development of digitalis toxicity may be the straw that breaks his marginal homeostasis and kills him. Where digitalis toxicity is not fatal, it may produce psychologic injury and result in the patient's refusal to cooperate in alternate therapy. Since elderly patients may be more sensitive to digitalis and more prone to develop toxicity, the choice of the proper digitalis preparation and its proper administration are important. In our hands, gitalin has proved to be an effective, safe, well-tolerated agent for this purpose.

The average digitalizing dose in fifty-three patients was 7.0 mg. The average daily maintenance dose was 0.92 mg. This maintenance dose, somewhat higher than reported by others, probably resulted from several factors peculiar to our facilities. In the first place, the majority of our early cases did not respond effectively to 0.5 mg. We therefore used 1.0 mg. routinely, with better therapeutic results and no more frequent toxicity. Secondly, our elderly cardiac patients were generally admitted with long-standing, far-advanced cardiac conditions which necessitated more intensive treatment. Many had greatly enlarged hearts and were in complete failure with slow sinus rhythm; others with rapid auricular fibrillation. In fourteen of seventeen patients refractory to other digitalis preparations, gitalin proved effective in restoring their heart compensation.

Various authors indicate that elderly patients with heart disease require smaller doses of digitalis than younger persons.[5,6] We are inclined to doubt this generalization, especially since few heart conditions are comparable and proper therapy must be individualized. Our own experience, based on this series and other patients as well, shows that many elderly individuals actually require more digitalis than younger persons with better myocardial reserve and shorter heart disease history. Furthermore, gastrointestinal changes in elderly persons may further interfere with the absorption of digitalis and necessitate larger doses. With the wider range gitalin offers, larger doses may be safely given without the attendant danger of serious toxicity.

At times, we deliberately gave gitalin to the point of toxicity. Since the signs of digitalis toxicity are not generally uniform, those most frequently encountered with gitalin merit some discussion. Slight nausea or anorexia was the first indication of approaching toxicity in our patients. Ventricular premature contractions frequently followed. None developed any other type of arrhythmia. Lowering the dosage or stopping the drug for a day or two usually eliminated these symptoms. Although neurologic signs have been ascribed to digitalis toxicity in elderly patients, we found none in this group.

Successful management of elderly patients with congestive heart failure requires not only a knowledge of cardiovascular dynamics and therapeutics, but also an appreciation that these people have additional extracardiac aging factors and associated disorders which further complicate their treatment. Multiphasic therapy of these cardiovascular disorders in geriatric patients, as described elsewhere, is essential.[7] Therapy should be planned to decrease the work of the heart, to increase myocardial efficiency, and to control the factors governing blood volume, especially salt and water retention.[8] The selection of a cardiac glycoside with a wide margin of safety, such as gitalin, and its proper administration in adequate dosage, are of inestimable value in treating congestive heart failure in elderly patients.

SUMMARY

1. Gitalin was used successfully in the treatment of congestive heart failure of seventy-seven patients with an average age of 78.4 years.

2. The initial gitalinizing dose in 155 trials ranged from 2.5 to 22.5 mg., averaging 7.0 mg. The daily maintenance dose ranged from 0.5 to 2.5 mg., averaging 0.92 mg.

3. Gitalin was generally well tolerated. Fifteen of seventeen patients refractory to other glycosides were adequately controlled with gitalin. Nausea, anorexia, and occasional ventricular premature contractions were the earliest indications of toxicity. No serious toxic effects occurred. No paroxysmal arrhythmias developed in this series despite doses calculated to produce toxicity.

4. Some differences between the problems of treating young and older patients with congestive heart disease are discussed.

5. Gitalin is a very useful cardiac glycoside for the treatment of congestive heart failure in elderly patients because of its wide therapeutic range and efficacy.

SUMMARIO IN INTERLINGUA

1. Gitalina esseva usate con bon successo in le tractamento de congestive disfallimento cardiac in septanta-septe patientes con un etate median de 78.4 annos.

2. In 155 essayos le dose initial de gitalinisation variava inter 2,5 e 22,5 mg. con un valor median de 7,0 mg. Le dose diurne de mantenentia variava inter 0,5 e 2,5 mg, con un valor median de 0,92 mg.

3. In general le toleration de gitalina esseva bon. Dece-cinque ex un serie de dece-septe patientes refractori a altere glycosidos obteneva adequate grados de controlo con gitalina. Nausea, anorexia, e a vices un prematur contraction ventricular esseva le prime indicationes de toxicitate. Nulle serie effectos toxic esseva notate. Nulle arrhythmias paroxysmal occurreva in le presente serie ben que le doses usate esseva calculate a resultar in toxicitate.

4. Es discutite alicunes del differentias inter le problemas del tractamento de juvene e de vetule patientes con congestive disfallimento cardiac.

5. Gitalina es un utilissime glycosido cardiac in le tractamento de congestive disfallimento cardiac de patientes de etates avantiate, tanto a causa de su extense spectro therapeutic como etiam a causa de su efficacia.

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Clinical Reports

SEPSIS LENTA LOCALIZED IN AN ARTERIOVENOUS ANEURYSM

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UP TO the present time, only a few cases have been described where an arteriovenous aneurysm became a septic focus. Still smaller is the number of cases where a radical cure of the sepsis was obtained by excision of the aneurysm.

In the medical literature which was available for us, we have found, from 1935 to 1952, ten cases of sepsis with a focus in an arteriovenous aneurysm which were successfully cured by surgical excision of the focus.

We are giving a concise data of all the cases in Table I. Besides these, a number of unoperated cases are described in the literature.[2-10]

The case reported here is the eleventh where sepsis was produced by an endarteritis in an arteriovenous aneurysm and where cure was obtained by surgical intervention.

CASE REPORT

History.—T.S.M., a 24-year-old country man, was directed as a war invalid to the Army Medical Academy (V.M.A.) on Oct. 12, 1950, because he had an aneurysm and kidney disease. Early in 1945, he had sustained a gunshot wound in the upper half of the right thigh (femoral region). The small entry wound healed rapidly. The larger exit wound was treated surgically (two days after the trauma) and healed without complications. Several days later, the patient noticed a painless thrill in the region of the entry wound. Evidently, this was the beginning of the aneurysm formation. There was no swelling of the leg, but later he experienced palpitations and exertional dyspnea.

Near the first of December, 1949, he became very ill. He had a 38° C. fever with marked sweating, weakness, and fatigue. He lost his appetite and about 8 kilograms in weight. Palpitations and dyspnea increased and he was unable to work. In the local country hospital, it was established that he had kidney disease and an aneurysm, following which he was sent to the V.M.A.

Clinical Findings.—The skin was very pale with a component of brown-yellow color. The heart was enlarged (see Figs. 1 and 2). The pulse was 98 per minute with a soft, systolic murmur at the apex and over the pulmonary area. Blood pressure was 130/40 mm. Hg. The liver and

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TABLE I

NO. CASE	AUTHOR	TYPE OF WEAPON	LOCATION OF ANEURYSM	EVENTUAL SOURCE OF SEPSIS	TIME FROM TRAUMA TILL SEPSIS (YEARS)	HEART CHANGES	HEMO-CULTURE	TREATMENT	TYPE OF OPERATION	ANATOMIC, HISTOLOGIC FINDINGS OF ANEURYSM	BACTERIOLOGIC FINDINGS ON OPERATED MATERIAL	RESULT
1	Rienhoff and Hamman,[1] U.S.A., 1935	Gun	External iliacal artery and vein	Tonsillitis	17	None	Streptococcus viridans	/	Excision	Vegetations and arteriosclerosis	Gram-positive streptococci	Healing of the sepsis
2	Touroff, Lande, and Kroop,[2] U.S.A., 1942	Gun	Femoral artery and vein	Dental extraction	9	?	Streptococcus viridans	/	Excision	Vegetations and arteriosclerosis	?	Healing of the sepsis
3	Lipton and Miller,[3] U.S.A., 1944	Gun	Femoral artery and vein	Sinusitis, dental extraction	15	None	Streptococcus viridans	/	Excision	Vegetations, endarteritis	Streptococcus viridans	Healing of the sepsis
4	Shumacker, Welford, and Carten,[4] U.S.A., 1946	Cannon	Femoral artery and vein	Tonsillitis	6 months	None	Streptococcus viridans	Penicillin 6 days 1.2 million units	Excision	Vegetations	Streptococcus viridans	Healing of the sepsis
5	Stojanović and Slavković,[5] Yugoslavia, 1948	Gun	External iliacal artery and vein	?	4	Systolic murmur, dilatations	Streptococcus viridans	Penicillin 28 days 11.2 million units	Excision, sympathectomy	Vegetations, thrombi, lymphatic infiltration	/	Healing of the sepsis
6	Statland and Orr,[6] U.S.A., 1949	Gun	Femoral artery and vein	Tonsillitis	18	Systolic murmur, dilatations	Streptococcus viridans	Penicillin 30 days 72 million units coronamide	Excision	Vegetations, arteriosclerosis, dead streptococci	Negative	Healing of the sepsis
7	Grimmault, L. and R.,[7] France, 1950	Gun	Femoral artery and vein	Suppurative calf ulcer	6	Systolic murmur, dilatations	Sterile	Penicillin sulfadiazin	Excision	/	Negative	Healing of the sepsis
8	Peter,[8] Germany, 1950	—	Femoral artery and vein	?	5	Combined aortic mitral disease, endocarditis	Sterile	?	Excision	Endarteritis	Nonhemolytic staphylococcus	Healing of the sepsis
9	Williams,[9] U.S.A., 1952	Barber's razor	Subclavian artery and vein	Influenza?	15	None	Streptococcus hemolyticus	Penicillin 23 days 19.2 million units	Resection of the vein, suture of the artery	Vegetations, endarteritis	?	Healing of the sepsis
10	Spohn and Pfeifer,[10] Germany, 1952	Shrapnel	Carotid artery	?	7	Systolic murmur, dilatations, gallop	?	Penicillin 2 million units	Excision	Verrucae vegetations, thrombi	Streptococcus viridans	Healing of the sepsis
11	Arsenijević, Ginzberg, and Najdanović. Yugoslavia, 1956	Gun	Femoral artery and vein	?	4	Systolic murmur, gallop, dilatations	Sterile	Penicillin 60 days 102.6 million units	Excision	Vegetations, thromboendarteritis	Streptococcus viridans	Healing of the sepsis

spleen were palpable 3 fingerbreadths below the costal margin. Anteriorly, in the upper third of the right femoral region, there was a punctiform cicatrix. Posteriorly, at the same level, there was a vertical cicatrix measuring 8.2 cm. At Scarpa's triangle a thrill was palpable. On auscultation there was a continuous murmur with systolic accentuation. The murmur was audible from the inguinal region down to the knee. Pulsations on the dorsalis pedis and posterior tibial arteries were palpable; however, they were less than in the left leg. The inguinal lymph nodes in the right inguinal region were hard and enlarged. Compression on the femoral vein in the region of the aneurysm produced an increase of the volumes of the pulse and filling of the arteries distal to the aneurysm (Brahmann's sign). Complete compression of the femoral blood vessels over the aneurysm produced the retardation of the pulse rate to 70 per minute and increased the diastolic blood pressure to 155/100 mm. Hg (positive Branham's sign). Venous pressure equaled 250 mm. water; after the compression of the aneurysm, it was 180 mm.

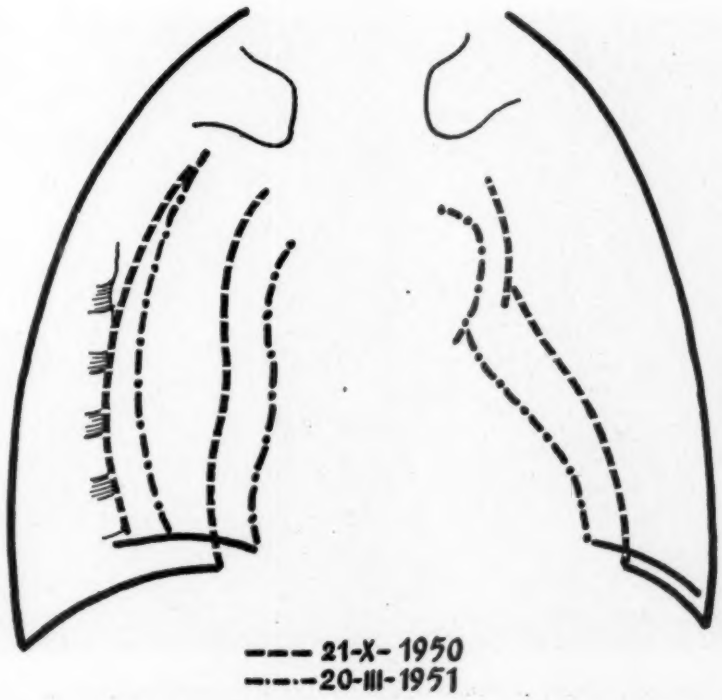

Fig. 1.—X-ray orthodiagrams of the heart before and after operation.

Laboratory Data.—ESR was 150/161 mm. (Westergren); Hemoglobin was 35 per cent; R.B.C. was 2,300,000; W.B.C. was 4,300; the differential revealed 6 per cent Stabs, 67 per cent Segs, and 27 per cent Lymphs. The urinalysis showed 1 Gm. per liter of albumin, cylindruria, hematuria (80 to 100 per high-power field), kidney cells, and W.B.C. 10 to 12. Blood urea was 1.056 gr.; NPN was 0.628 gr. % per liter; Cl was 3.621; NaCl was 5.967; proteins were 68.17 (albumin, 26.04 and globulin, 42.13); Weltmann showed 11 tubes; Takata test was positive; and Kürten test (formogel) was positive also. Wassermann serial readings were negative. X-ray orthodiagram (Fig. 1) and teleroentgenogram (Fig. 2) of the heart showed considerable enlargement. ECG showed no considerable alterations. The serial blood cultures were negative.

Diagnosis.—Evident signs of complicated sepsis with manifestations of hemorrhagic nephritis and renal insufficiency, severe anemia, enlarged spleen, and other signs described presented great similarity to endocarditis lenta. However, the course and other factors led to the suppositions that the seat of the sepsis was not in the endocardium, but in the aneurysm. The absence of

earlier heart disease, the presence of a systolic murmur which disappeared before the operation, and significant enlargement of the heart did not signify in themselves cardiac valve damage, but it could be explained as the result of well-known hemodynamic changes following an arteriovenous fistula. On the basis of all these findings, we concluded that this was a case of an arteriovenous aneurysm with secondary hemodynamic changes, and sepsis lenta with the focus being in the aneurysm. The patient was given penicillin therapy as a preparation for surgical intervention and to improve his general condition.

Treatment.—For two months prior to operation, from Oct. 26, 1950, the patient received a total of 102,600,000 units of penicillin. In the first week, the daily dose was 1,000,000 units, but since this was not effective, the daily dose was increased to 2,000,000 units. During this preparation for operation, the signs of anemia were less evident, the patient's weight increased, and he became afebrile. The heart size remained unchanged since admission, but the murmur and gallop rhythm disappeared. Blood pressure was the same, pulse was 84 per minute, and the liver

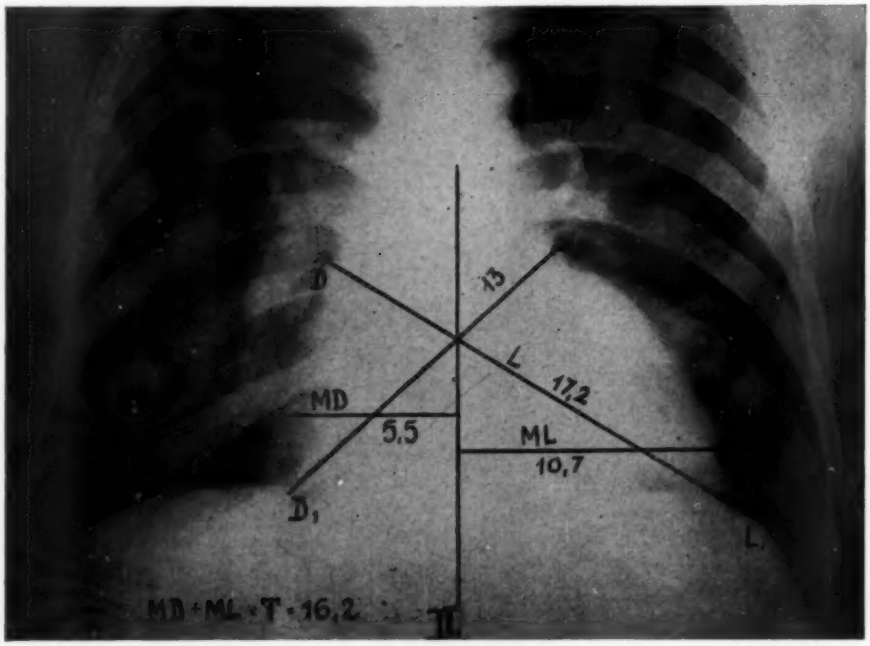

Fig. 2.—X-ray teleroentgenogram of the heart before operation.

and spleen were smaller (1 fingerbreadth). The sedimentation rate was 77/120 mm.; R.B.C. was 3,900; Hb was 50 per cent; the urine showed R.B.C. 5 to 6 per high power field and W.B.C. 8 to 10 per high power field; the urea and the other biochemical analyses of the blood were normal. The blood proteins were still 68.9 but now albumin was 41.2 and globulin was 27.7 Gm. However, the Weltmann, Takata, and the Kürten (formogel) tests remained positive.

The arteriogram showed a very well-developed collateral circulation with a particularly enlarged profunda femoral artery. The Moschcowitz test also revealed good collaterals; skin hyperemia showed after forty-five seconds.

Operation.—Excision of the aneurysm with ligature of the proximal and distal blood vessels was performed on Dec. 25, 1950, under spinal anesthesia, later combined with general ether and oxygen anesthesia. The operation was complicated by very hard cicatricial tissue around the aneurysm and by hemorrhage from abundant dilated collaterals. Compression of the main blood vessels was performed before excision and it was confirmed that the leg did not become ischemic. The femoral arteries and veins were much dilated, to the size of the third finger proximate from the aneurysm, with very fragile walls. At one point in the operation, an incomplete transverse

rupture of the femoral artery proximal to the deep femoral artery occurred. In order to save the main collaterals, this rupture was ligated by an individual suture. The femoral artery was ligated just distal to the point of division with the deep femoral artery. The blood vessels distal to the aneurysm were considerably narrowed (pencil-sized). It was interesting to note that the enlargement of the femoral artery did not extend as far as the fistula, but only to the origin of the femoral artery, where the artery narrowed rapidly on its way to the aneurysm. Powerful pulsations of the distally ligated portion of the artery (Lexer-Cönen-Henle's sign) where shown after excision (see Fig. 3).

The aneurysm was on the lateral wall of the resected artery. It was like a cherry, about 1 cm. in diameter, and against it was an arteriovenous fistula passable by the tip of the finger. The preparation was resected on the operating table and then there were seen numerous vegetations, 1 to 2 mm. in dimension, so that the internal surface of the preparation was uneven. One piece of the intima was crushed and bacterial culture was made, in which grew *Streptococcus viridans* sensitive to penicillin, streptomycin, and Aureomycin.

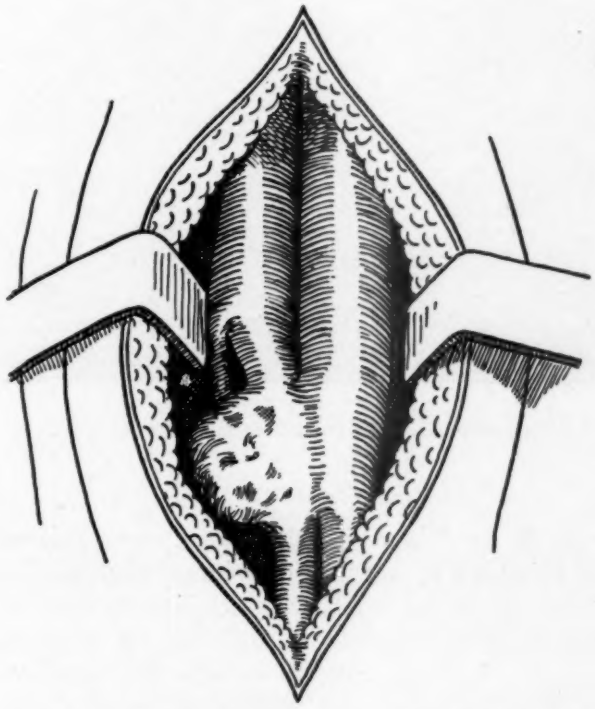

Fig. 3.—Topographic situation on the operated field.

Histologic examination showed subacute thromboendarteritis (Brankovan) (Fig. 4).

Postoperative Course.—Pulse of the dorsal artery of the foot was palpable immediately after the operation, and after the fourth day it was equal to the pulse of the left leg. Arterial pressure on the first day was 150/110 mm. Hg. On the fifth day, there appeared swelling of the leg without signs of a thrombophlebitis. This swelling disappeared completely after eight days. During the twenty-four days after the operation, 28,400,000 units of penicillin were given. All the signs of the sepsis disappeared gradually (Fig. 3). The patient became afebrile after a short postoperative period. Sedimentation rate became normal. R.B.C. was 4,290,000 and hemoglobin was 72 per cent. Weltmann and Takata tests were normal. Kürten test was negative. Renal function and urine findings were normal after severe hematuria with renal colic and excretion of fine calculi. Enlargement of the liver and of the spleen disappeared. The heart resumed normal

configuration and size. Arterial pressure stabilized at 120/80 mm. Hg and venous pressure fell to 110 mm. water. The patient gained weight constantly and on March 23, 1951, was dismissed from the Clinic as healthy. Later, he came for checkup. He feels healthy and is able to do a normal amount of work. At checkup, all the findings show their normal state.

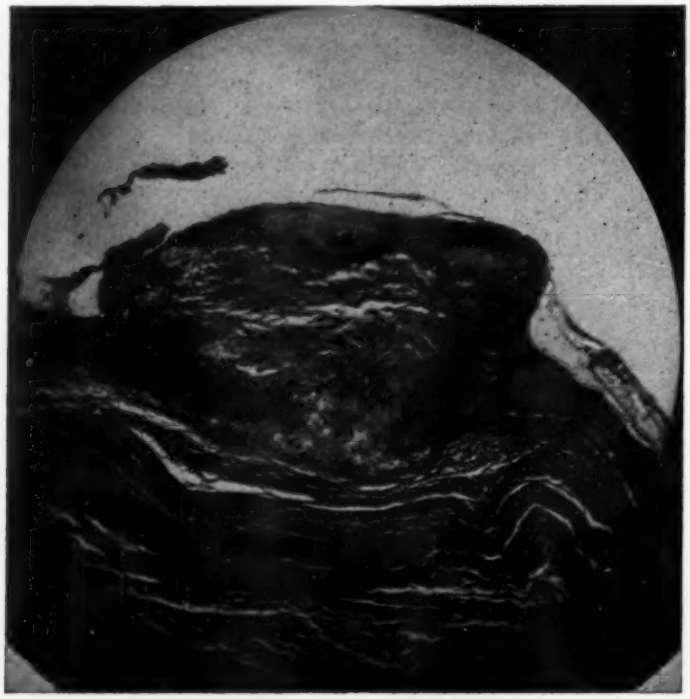

Fig. 4.—Photomicrograph of thromboendarteritis subacuta (see text).

COMMENTS

This case is the eleventh in which the seat of the sepsis was removed and a complete cure was obtained by surgical excision of the arteriovenous aneurysm. If, besides the eleven described cases, we take into account a small number of cases unoperated upon or discovered by autopsy, we may conclude that it is, in fact, a rare disease. It is not easy to explain this conclusion when we take into consideration that, in the period from 1935, when the first case was presented, throughout the Second World War there were at least 10,000,000 wounded.

SUMMARY

1. A case of sepsis lenta which was cured by excision of a traumatic arteriovenous aneurysm was presented. It and the other analogous cases from literature were discussed.

2. Arteriovenous aneurysm associated with a sepsis must be considered as an absolute indication for surgical intervention. Noninfected arteriovenous aneurysms must be cured surgically also, so that they do not produce greater hemodynamic changes, because such disturbances must be considered as predilected points for formation of a septic focus.

3. The treatment with the antibiotics cannot replace the surgical intervention because this treatment does not always sterilize the focus. But, in the

more severe cases, it must be considered as a useful means for retardation of the sepsis and preparation of the patient for the operation.

4. The operative procedure of choice is the excision of the aneurysm to the healthy tissue with maximal saving of the collaterals, because of the principle that the septic focus must be removed completely and radically. Only when there is danger of ischemia as the result of this procedure, due to underdeveloped collaterals, may a palliative procedure which does not disturb the passage of the main arterial tree be employed.

SUMMARIO IN INTERLINGUA

1. Es presentate un caso de sepsis lente que esseva curate per le excision de un traumatic aneurysma arteriovenose. Le caso es discutite insimul con altere casos analoge ab le litteratura.

2. Aneurysma arteriovenose associate con sepsis debe esser considerate como indication absolute pro intervention chirurgic. Non-inficite aneurysmas arteriovenose debe etiam esser curate per intervention chirurgic a fin que illos non pote producer major alterationes hemodynamic. Tal disturbationes debe esser considerate como sitos favorite pro le formation de focos septic.

3. Le tractamento a antibioticos non pote reimplaciar methodos chirurgic proque antibioticos non succede in omne casos a sterilisar le foco. In le plus sever casos, nonobstante, illos debe esser considerate como utile medios pro retardar le sepsis e preparar le patiente al operation.

4. Le chirurgia de election es le excision del aneurysma usque al histos san con preservation maximal del collaterales. Le principio guidante es le necessitate del ablation complete e radical del aneurysma. Un procedimento palliative que non disturba le passage del major arbore arterial es acceptabile solmente in casos in que un intervention radical apportarea le risco de ischemia.

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COARCTATION OF THE ABDOMINAL AORTA

REVIEW OF THE LITERATURE

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COARCTATION of the abdominal aorta is a rare condition, having been previously reported thirteen times. The purpose of this paper is to report an additional case and to review the literature on this subject.

CASE REPORT

A 32-year-old white housewife had had severe hypertension for several years, first discovered during her first pregnancy in 1936. This pregnancy and four succeeding ones terminated in spontaneous miscarriage, and on each occasion she was thought to have eclampsia. She had had intermittent claudication in the calf muscles of both legs for six years, and had undergone a bilateral lumbar sympathectomy one and one-half years before the present illness without relief. Treatment with priscoline had not given benefit. Just prior to her admission to the hospital she was able to walk only one block before being forced to stop because of pain in the calf muscles and feet. Trophic changes of the toes had occurred and one year before this study she had been troubled by an area of gangrene on the right great toe. This patient also suffered from frequent occipital headaches, occasional nausea and vomiting, and shortness of breath on exertion.

The patient had been pregnant for four months when on May 18, 1951, she suffered sudden onset of nausea and vomiting, severe occipital headache, marked blurring of vision, and went into general collapse. She was admitted to an Army hospital where it was noted that she was mentally unresponsive, her eye movements were uncoordinated, and nuchal rigidity was present. The retinal fundi revealed hemorrhages, exudates, and papilledema. Blood pressure was 210/110 mm. Hg in the upper extremities, and 100 systolic in the lower extremities. The pulses were so weak in the femoral and popliteal arteries as to render determination difficult. Pulses were not palpable below the popliteal vessels. The heart was enlarged to the left on percussion and a moderately loud systolic murmur was present at the apex. High in the epigastrium a good aortic pulse could be felt, but this could not be followed downward. A systolic bruit was audible about the umbilicus and was also present in the back overlying the eleventh thoracic vertebra. The abdominal findings were otherwise compatible with the state of pregnancy. Marked plantar and pulmar erythema was noted, and there was also an enlargement of the terminal phalanges, which had a cherry red color.

A spinal puncture produced grossly bloody fluid. Laboratory examinations showed a moderate and persistent albuminuria, occasional leukocytes, erythrocytes, and granular casts in the urine. At the time of admission to the hospital the blood leukocyte count was 19,450 per cubic millimeter, hemoglobin was 13.2 Gm. per 100 c.c., and the hematocrit 45 per cent. The Kahn test was negative, as was the spinal fluid Wassermann. Blood chemistry studies revealed nonprotein nitrogen of 49 mg. per cent, creatinine 2 mg. per cent, and chloride 101 meq. per liter.

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X-ray views of the skull were normal. A roentgenogram of the chest revealed moderate cardiac enlargement predominately of the left ventricle. X-ray views of the abdomen revealed a twin pregnancy but were otherwise not remarkable. Electrocardiograms showed left axis deviation and were within normal limits.

The patient was transferred to Letterman Army Hospital on May 24, 1951, and was treated conservatively for cerebral hemorrhage. Spinal fluid gradually cleared and by June 2, 1951, was clear and slightly xanthochromic. The spinal fluid erythrocyte count had reduced from 167,000 to 1,550 per cubic millimeter. The patient continued to complain of severe headache throughout this period. At a combined staff conference, decision was made to evacuate the uterus in the hope of preventing a fatal outcome of the patient's illness. This was accomplished on June 5, 1951, by cesarean section. After operation the patient's general condition continued to improve, but the blood pressure remained elevated (220/140 mm. Hg in the arms). The patient's mental state improved. Headaches became less frequent.

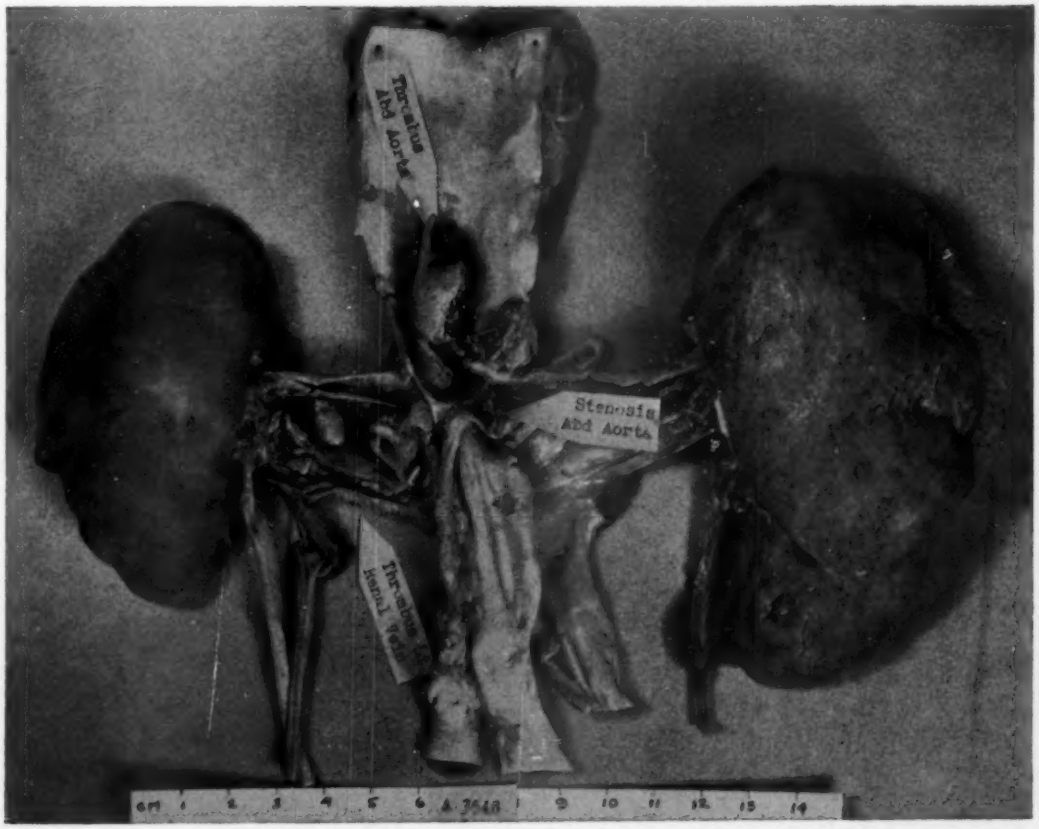

Fig. 1.—The principal post-mortem findings are illustrated. Note the relationship of the narrowed segment to the origin of the renal arteries and the thrombus adherent to the wall of the aorta just above the coarctation.

Suddenly on the ninth postoperative day the patient complained of severe, crushing, substernal pain and she became cold, cyanotic, and poorly responsive. The pulse rate increased to 160 per minute and became thready in quality. The blood pressure dropped to 190/90 mm. Hg. Mephenteramine sulfate was administered with brief temporary improvement in blood pressure. The lung fields, which were initially clear to examination, gradually became filled with moist râles. The patient's condition continued to deteriorate and her blood pressure fell to 80/62 mm. Hg in the arms. No further response from supportive drugs could be obtained and the patient died.

At autopsy the aorta was found to be sharply constricted just below the origin of the renal arteries (Fig. 1). At the point of maximum constriction the aorta measured 2 cm. in the outside circumference as compared to its size at the aortic valve, which was 6 cm. in circumference. The area of constriction was quite localized to the immediate site of the renal artery orifices. There was no demonstrable poststenotic dilatation. The aorta was small and hypoplastic below the site of constriction. A few atherosclerotic plaques were noted in the abdominal aorta proximal to the coarctation, but none were found distally. A smooth, pale, friable thrombus extended upward from the point of narrowing, along and adherent to the left aortic wall occluding the orifice of the left renal artery. The thrombus impinged upon the orifice of the right renal artery but was not adherent to it. A small area of patency of the aortic lumen persisted. Examination of the brain revealed the presence of old subarachnoid hemorrhage but there were no visible bleeding points and no aneurysms were present. The findings in the lungs were those usually associated with congestive heart failure. The heart weight was only 355 grams and the left ventricular wall was 1.5 cm. thick.

REVIEW OF THE LITERATURE

In 1847, Quain[1] described the first case of coarctation of the abdominal aorta. His patient was a 50-year-old man who complained of epigastric pain on exertion during the last year of life, having been asymptomatic previously. The patient died suddenly and at autopsy a coarctation ½ inch in length situated immediately below the origin of the renal arteries was found. In 1861, Powers[2] described the case of a 17-year-old boy who died following a convulsion. This patient had had a history strongly suggesting acute rheumatic fever several years prior to death. At autopsy there was marked narrowing of the aorta and iliac arteries. The narrowing of the aorta began below the inferior mesenteric artery. Enlarged tortuous internal mammary and superior epigastric arteries were also present.

There followed a lapse of seventy-six years without a reported case. In 1937, Maycock[3] reported the case of an 18-year-old girl who complained of dyspnea and occasional exertional pricking chest and shoulder pain. On examination the patient was found to have a blood pressure of 200/89 mm. Hg in both arms and 120/110 mm. Hg in the legs. A bruit was heard in the back, from the level of the tenth thoracic to the third lumbar spines. She was followed for four years during which time she gradually developed weakness in her lower extremities, mild cardiac enlargement, and visibly pulsating internal mammary and superior epigastric arteries. She also developed unrelated amebiasis which eventually led to her death. At autopsy there was mild left ventricular hypertrophy, but no visible structural valvular lesion. A saccular aneurysm of the aortic arch was described. At a point 1.5 cm. below the renal arteries the aorta abruptly became narrowed to a cord 8 mm. in diameter and 3 cm. long, the lumen of which was filled with a firm gray thrombus. The aorta thereafter became normal in size, as were also the iliac arteries. The author suggested that the defect might be due to "lack of proper fusion of the original two dorsal aortas with regression and loss of one of them."

Baylin[4] reported anatomic findings in a 32-year-old man in whom the coarctation occurred below the renal arteries. He did not report clinical features in detail, but the patient manifested no cardiovascular symptoms so far as it is determinable. At autopsy, the principal findings were multiple aneurysms of the aorta below the renal arteries. These aneurysms were filled with organized, calcified thrombus. At the level of the second pair of lumbar arteries the coarcted aorta was completely occluded. Extensive anastomoses involving the superior mesenteric, inferior and superior epigastric, and internal mammary arteries were described.

In one of the cases of coarctation of the aorta reported by Steele[5] the constriction was at and slightly above the level of the renal arteries. This interesting patient was first observed in 1922 at 29 years of age, because of complaints of headache and dizziness; she had been found to be hypertensive one year before. She remained essentially well and had good renal function on each periodic examination until 1937, at which time congestive heart failure developed. In 1938, she had a right hemiplegia and died following another cerebrovascular accident in 1939.

One of the two unusual cases of aneurysms of the aorta reported by Bahnson, Cooley, and Sloan[6] concerned a patient in whom narrowing of the aorta occurred just below the renal arteries.

This 35-year-old woman had been found to have hypertension at 28 years of age on routine physical examination. One year later she developed intermittent claudication. At the age of 31, headaches and dizziness appeared and a supradiaphragmatic and splanchnic sympathectomy was performed, followed by temporary subjective relief. For one year prior to her final admission to the hospital, she had evidence of congestive heart failure and occasional attacks of angina pectoris. Angiocardiography revealed a complete occlusion of the aorta below the renal arteries. Studies demonstrated markedly reduced blood flow to the lower extremities. In 1948, a second surgical operation was performed. The aorta was found to taper to a point of occlusion just below the renal arteries. Distal to this point, the aorta was again patent and apparently normal. A lumbar sympathectomy was performed, with resultant slight improvement.

Kondo and associates[7] described the case of a 12-year-old girl who came to them in November, 1946, because of lassitude and weakness of three years' duration. The right radial and both femoral arterial pulsations were absent. A systolic murmur was found periumbilically and in the upper lumbar areas. A thrill and murmur was found in the right supraclavicular fossa. The patient's course was one of progressive cardiac failure leading to death one month after she was first observed. At autopsy the principal findings were: signs of congestive heart failure, left ventricular hypertrophy, hypoplastic subclavian arteries, and a marked, sharply defined coarctation of the aorta between the celiac axis and the renal arteries. Of additional interest was the finding of a protruding, valve-like area of intimal proliferation at the coarctation site.

Wang[8] described the case of a 56-year-old man who had been known to have cardiovascular disease for seven years. He had been found to have congestive failure three years prior to death. His last admission to hospital was because of pulmonary infarction. He developed multifocal ventricular premature beats and died shortly thereafter. At autopsy a mural thrombus in the left ventricle was found, as well as several pulmonary infarcts and splenic infarcts. In the abdominal aorta a narrowing 4 cm. long was noted 10 cm. above the bifurcation of the aorta. The narrowing began 3 cm. above the renal arteries and was of hourglass configuration, with a circumference at the isthmus of 1.2 cm. Extensive atherosclerosis in the region of the coarctation was described.

Doumer[9] and his associates described the case of a 40-year-old man who had suffered from intermittent claudication for eleven years prior to their examination. Hypertension had been known to be present for three years. The electrocardiogram revealed left ventricular hypertrophy. An intravenous pyelogram revealed normal function of the right kidney but none of the left. Retrograde pyelograms were normal bilaterally, although the left kidney was noted to be smaller than the right. Aortography revealed a sharp obstruction to the dye column at the level of the renal arteries. The right renal artery was well visualized but the left was not visualized. A left nephrectomy was performed with no beneficial results.

Goldzieher[10] and his associates reported a case which presented features resembling those of pheochromocytoma. Their patient was a 45-year-old woman with a strong family history of hypertension, who complained of attacks of nausea, vomiting, pressure sensations in the posterior cervical region, and temporary unconsciousness, and were followed by polyuria. These attacks had been occurring several times each week for a period of six years. When her symptoms first began she was found to have hypertension but she was known to have had normal blood pressure two years earlier. During attacks her blood pressure was recorded as high as 230 mm. Hg systolic, whereas it was found to be normal in intervals between attacks. Surgical exploration revealed a coarctation of the abdominal aorta at the level of the renal arteries. A rich collateral vascular plexus above the level of the coarctation involved the blood supply to the adrenal glands but no adrenal tumor was found.

In 1952, Fischer and Corcoran[11] reported the case of a 14-year-old boy who came to them because of lancinating flank pain, headaches, and diminished visual acuity. He was found to have hypertension and left ventricular hypertrophy. Funduscopic examination revealed hemorrhages, exudates, and papilledema. The patient failed to respond to medical management and was surgically explored. A small right kidney and pulseless right renal artery were noted. The right kidney was removed but the patient failed to improve. At autopsy the aorta was found to be narrowed at the level of the renal arteries. The diameter at that level was 2.5 cm., whereas it was 3.7 cm. at the level of the superior mesenteric artery. The latter vessel was markedly enlarged and tortuous. There was intimal thickening of the aorta at the level of both renal arteries. This thickening had reduced the lumina of the renal arteries to caudally directed slits.

One of the three interesting and unusual cases of coarctation reported by Froment and associates[12] was that of a 32-year-old woman who had been seen repeatedly by physicians since the age of 18, and had not been found to have hypertension until the age of 31. At that time she complained of nervousness, fatigability, and a sensation of heaviness in her lower extremities. Her blood pressure was 170 mm. Hg systolic. In 1951, the patient's symptoms were worse and her blood pressure had risen to 230/130 mm. Hg, but femoral artery pulsations were barely palpable. A systolic bruit was heard over the back at the level of the second lumbar vertebra. An aortogram was made, which revealed complete stenosis of the aorta between the first and second lumbar vertebrae. The left renal artery was well visualized but the right was not filled. Because of the level of the obstruction surgery was not performed. While the authors considered this a case of coarctation of the aorta, this is not proved.

In 1953, Albanese and Baila[13] reported the case of a 12-year-old girl who came to medical attention when she developed scarlet fever. Her physician heard a heart murmur and Dr. Baila was asked to see the patient. He found a loud systolic murmur over the first lumbar vertebra posteriorly. Pulsations were absent in the abdominal aorta and below. The blood pressure was 210/130 mm. Hg in the arms. An angiocardiogram suggested a typical coarctation of the aorta at the third portion of the arch of the aorta. However, a retrograde aortogram performed through the right femoral artery revealed poor filling of the renal arteries and no filling of the aorta above the renal arteries. Surgical exploration revealed a slight narrowing of the lower thoracic aorta and a coarctation of the aorta beginning just below the diaphragm. The aorta and all of its branches were hypoplastic from that point downward. The renal arteries were only 2 mm. in diameter. The surgeon inserted a homologous graft below the renal arteries. Postoperatively the patient developed anuria and encephalopathy and died.

DISCUSSION

Analysis of the reported cases of coarctation of the abdominal aorta permits certain comments. Since, however, there have been only fourteen such cases, no statistical inferences can be drawn.

The average age of such patients at the time of diagnosis was 32 years. The average age of death of those cases proved by autopsy was 29 years. Sex does not appear to be a factor, nor does race. In these particulars coarctation of the abdominal aorta does not differ greatly from coarctation of the thoracic aorta.

It is of interest to note that in ten of the fourteen cases the site of the coarctation was at or below the origin of the renal arteries. In our case there was also a thrombus in the aorta just proximal to the site of the coarctation. This has been noted in other cases reported.[3,4] The collateral circulation in cases of coarctation of the abdominal aorta is highly variable and does not appear to correlate closely with the site of the coarctation. However, the presence of demonstrable collateral arterial circulation in the abdominal wall favors the diagnosis of coarctation somewhere within the abdominal aorta. A systolic bruit over the lumbar area has been noted in several cases and may be a helpful sign when present.

Symptoms in the legs resembling intermittent claudication were reported in five of the cases. This appears to be a higher incidence than is found in cases of coarctation of the thoracic aorta. On the other hand, it is interesting to note that so few had intermittent claudication and that none had symptoms referable to the buttocks or thighs. In all cases in which there were symptoms referable to the legs, the narrowed segment was at or below the renal arteries.

Angiography, particularly translumbar aortography, appears to be the roentgenographic diagnostic method. Aortography permits an accurate deline-

ation of the site of the coarctation, its relationship to the origin of the renal arteries, and the length of the narrowed segment. These data are essential to the decision to attempt surgical correction. It appears probable that the increasing use of angiography may lead to more frequent discovery of cases of coarctation of the abdominal aorta.

The most important factor in determining the operability of cases of coarctation of the abdominal aorta is the relationship of the narrowed segment to the renal arteries. This relationship is so close in the majority of cases that surgical excision is hazardous.

SUMMARY

A case of coarctation of the abdominal aorta is presented and the literature, consisting of thirteen cases, is reviewed.

Coarctation of the abdominal aorta is a rare condition which presents certain features which differ from coarctation of the thoracic aorta. These features are: a systolic bruit heard best in the abdominal and lumbar regions, and complaints of intermittent claudication in the lower extremities.

Translumbar aortography appears to be the best definitive diagnostic method.

Surgical excision is complicated by the frequent close proximity of the renal arteries to the narrowed segment.

SUMMARIO IN INTERLINGUA

Es presentate un caso de coarctation del aorta abdominal. Le litteratura, consistente de reportos de 13 casos, es revidite.

Coarctation del aorta abdominal es un condition rar que presenta certe aspectos differente ab coarctation del aorta thoracic. Iste aspectos es: un ruito systolic que es melio audibile in le regiones abdominal e lumbar e reportos de claudication intermittente in le extremitates inferior.

Il pare que aortographia translumbar es le melior methodo de diagnose definitive.

Le excision chirurgic es complicate a causa del frequentemente stricte proximitate del arterias renal.

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Announcements

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE—in effect the educational division of the Cleveland Clinic Foundation—offers a TWO-YEAR TRAINEESHIP IN CARDIOVASCULAR DISEASE oriented toward research and academic practice. It is available to physicians who have completed an approved internship and at least two years of approved residency training in Internal Medicine or two years of approved residency training in Pediatrics. The program is unique in that it is designed to give the widest possible coverage of the field. The two years are divided into three periods of eight months each. These are spent, respectively, in the study of cardiovascular-renal disease in the Research Division, and in general cardiology and pediatric and surgical cardiology in the Division of Medicine. In each field the trainee will be responsible for a specific research project. Responsibility for training is in the hands of Drs. Irvine H. Page, A. C. Corcoran, and Harriet Dustan (Research Division) and Drs. A. Carlton Ernstene, William Proudfit, and F. Mason Sones, Jr. (Division of Medicine). The program will be coordinated by Dr. Charles L. Leedham, Director of Education, Frank E. Bunts Educational Institute, 2020 East 93rd Street, Cleveland 6, Ohio, to whom inquiries should be addressed. The program is planned for six trainees (three appointed each year), the appointments to run from July 1, 1956.

The 1956 CONFERENCE OF THE AMERICAN OCCUPATIONAL THERAPY ASSOCIATION will be held from September 29 through October 5 in Minneapolis, Minnesota, at the Nicollet Hotel.

The theme of the conference will be "Time for Reflection," and the topics will include: Occupational Therapy in Relation to General Medicine and Surgery, Geriatrics, Pediatrics, Physical Disabilities, and Psychiatry.

A SYMPOSIUM ON ELECTROLYTES AND THE CIRCULATION will be held in Burlington, Vermont, on Sept. 8 (afternoon), Sept. 9 (all day), and Sept. 10 (morning), 1956, under the sponsorship of the Vermont Heart Association and the University of Vermont College of Medicine. It will be devoted to the electrolyte metabolism in congestive heart failure and the role of electrolytes in myocardial metabolism, the electrocardiogram, and cardiac arrhythmias, as well as vascular reactivity and hypertension. The guest speakers will include: Drs. S. Bellet, Ch. McC. Brooks L. Grumbach, S. Hajdu, B. F. Hoffman, A. Kunin, E. J. Leonard, K. I. Melville, A. J. Merrill, A. S. Relman, and R. Tarail. Members of the University of Vermont faculty participating in the Symposium will be: Drs. E. L. Amidon, J. H. Bland, E. Lepeschkin, W. Raab, W. V. B. Robertson, F. Sichel, E. A. H. Sims, B. Surawicz, and C. M. Terrien. Further information can be obtained from Dr. Eugene Lepeschkin, University of Vermont College of Medicine, Burlington, Vermont. The Symposium is open to all interested persons.

APPLICATIONS FOR AWARDS available July 1, 1957, will be received by the LIFE INSURANCE MEDICAL RESEARCH FUND as follows: (1) Postdoctoral research fellowships, until Oct. 15, 1956. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend $3,800, with allowances for dependents and necessary travel. (2) Grants to institutions in aid of research on cardiovascular problems, until Nov. 1, 1956. Support is available for physiologic, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Approximately $1,000,000 will be available for the two types of awards. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

THE SEVENTH CONGRESS OF THE PAN-PACIFIC SURGICAL ASSOCIATION will be held in Honolulu, Hawaii, Nov. 14 to 22, 1957. All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

An outstanding scientific program by leading surgeons with sessions in all divisions of surgery and related fields promises to be of interest to all doctors.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Room 230, Young Building, Honolulu, Hawaii.